DIAMETER OF ERYTHROCYTES (MICRONS)

Horse	5.6
Mule and ass	5.3
Ox	5.6
Sheep	5.0
Goat	4.1
Pig	6.2
Dog	7.3
Cat	6.5
Man	7.5

Hubacek has reported on the size of erythrocytes of domestic animals, including the ranges of variation.

Number. In enumerating blood corpuscles the number is determined per cubic millimeter of blood. The figures given on p. 23 illustrate the average erythrocyte numbers in the blood of the domestic animals according to the work of several authors [Kuhl, Welsch, Fritsch, Baker, Wintrobe, Miller, Mayerson, Landsberg (1940), Barlow and Biskind].

These figures reveal that the number of erythrocytes varies greatly among the different species. The number is subject also to rather wide variations within the species, as is shown, for the dog, in Fig. 1. In fact, the number is not at all constant in the individual. Among the factors responsible for intraspecific or intraindividual variations are age, sex, environment, exercise, diet, and climate.

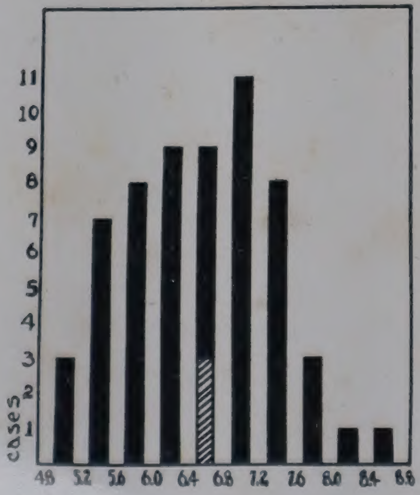

FIG. 1.—Average erythrocyte counts (millions per cubic millimeter) in the blood of sixty normal dogs. (From Mayerson, *Anatomical Record*, published by the Wistar Institute.)

The observation has been made (Macleod and Ponder) that thoroughbred horses have a significantly higher erythrocyte count and hemoglobin content in their blood than have cold-blooded horses. The higher values in thoroughbreds are present at birth and are maintained in the various age groups. It is believed therefore that the higher erythrocyte numbers and hemoglobin contents represent a genetic characteristic of the thoroughbred.

The erythrocyte count of mules is practically the same as that of horses (Morris).

Marked variations in erythrocyte counts may occur in pathological conditions. For some of these, and for the methods of counting blood corpuscles, consult the book by Coffin or the monograph by Holman.

NUMBER OF ERYTHROCYTES IN BLOOD (MILLIONS PER CUBIC MILLIMETER)

Horse	6.9
Cow	6.3
Sheep (lambs)	10.1
Sheep (over 1 yr. old)	8.1
Goat	13.9
Pig	7.4
Dog	6.2
Cat	7.2
Rabbit	5.9
Cock	3.2
Hen	2.8
Pigeon	4.0
Man	5.4
Woman	4.8

Corpuscular Surface. The total surface presented by the erythrocytes of the body can be estimated when the blood volume, erythrocyte count, diameter, and thickness are known. The results are amazingly large. The accompanying table gives such estimates, which are of interest from the standpoint of the respiratory or gas-transport function of the blood. Further examination of the table shows that there are, in different species, 27 to 36 square meters of corpuscular surface for each kilogram of body weight. The lowest figure is for the goat, the highest for man.

ESTIMATED TOTAL ERYTHROCYTE SURFACE (PAECHTNER)

Species	Weight	Erythrocyte Surface	Erythrocyte Surface, sq. m. / Body Weight, kg.
	kg.	*sq. m.*	
Man	70	2,500	36
Horse	500	14,000	28
Ox	500	16,000	32
Sheep	40	1,280	32
Goat	30	800	27
Pig	100	3,000	30

The figures for erythrocyte surface become more impressive when they are compared with the body surface area: that of a man of average size is less than 2 square meters; that of a 500-kg. cow somewhat less than 5 square meters.

Suspension Stability. It was stated above that when a sample of blood in which coagulation has been prevented is allowed to stand, the red corpuscles settle to the bottom, the plasma rises to the top, and the white corpuscles occupy a thin intermediate zone. However, the rate of sedimentation of the erythrocytes varies greatly among the different species. Erythrocytes in horse blood settle quickly and the *suspension stability* of such blood is said therefore to be slight, whereas in ruminants the suspension stability is great and the rate of settling slow. The rate of sedimentation is measured, in standard tubes, by the distance in millimeters through which the uppermost layer of corpuscles passes in a certain time, usually one hour.

In normal horses Hammersland and co-workers observed an average sedimentation rate of 18 mm. per hour, whereas in horses suffering from infectious anemia the average rate was 26 mm. Griffin and Brose have also noted an increase in the sedimentation rate in equine infectious anemia. The acceleration was greatest at the time of the highest body temperature or following it. Nichols has recently devised an automatic photographic device for recording the rate of sedimentation and has worked out a satisfactory technic for horse blood. His publications include an extensive survey of the literature on sedimentation of erythrocytes.

The sedimentation rate of cattle blood is low. Ferguson (1937) found a mean rate of 2.4 mm. in seven hours. He considered a value over 4 mm. as indicative of a pathological condition.

In normal dogs Simms records sedimentation rates of 1 to 4 mm. per hour. The rate was greater in canine distemper, salmon poisoning, and usually in pregnancy.

Tentative normal sedimentation rates for domestic animals are given by Coffin.

Fåhraeus, who has made a detailed study of suspension stability, found that changes in the viscosity of the plasma, the specific gravities of the corpuscles or plasma, or the size of the corpuscles have practically nothing to do with the sedimentation rate. The only factor of importance is the degree of agglutination of the erythrocytes, and it is certain that the plasma proteins markedly influence this factor. According to some workers it is an increase in the fibrinogen content of plasma that hastens agglutination and settling, while according to others it is an increase in the globulin. Apparently the increase in fibrinogen is more important (Nichols, 1942a).

It has been suggested that variations in the concentration of the blood proteins affect the sedimentation rate by variations in the colloidal state of the plasma and hence in the electric charges on the proteins and red cells (Ropes, Rossmeisl, and Bauer).

That the composition of the corpuscles themselves may be a factor of importance, at least in some animals, is suggested by the observation that the corpuscles of horse blood settle almost as rapidly in ox plasma as in horse plasma, in spite of the fact that the ox is a species in which sedimentation is slow (Krumbhaar, 1928).

In the manufacture of clear hog cholera antiserum, bean extract is used to agglutinate the erythrocytes and thus to facilitate their sedimentation (Dorset and Henly).

Composition. The details of the composition of erythrocytes in many species of domestic animals are given in the table on p. 53. It will be noted that in different animals the red corpuscle is made up, in round numbers, of—

Water	59-64 per cent
Total solids	36-41 per cent
Hemoglobin	30-33 per cent

Examination of these figures shows that stroma (total solids minus hemoglobin) constitutes 6 to 8 per cent of the corpuscles. Stroma consists mainly of protein, the lipids lecithin and cholesterol, and inorganic salts. The lipids are believed to play an important part in giving unity to the corpuscle, and the older evidence indicated that they were concerned in regulating the permeability of its peripheral membrane, through which water and anions easily pass but cations less readily or not at all. Newer evidence has failed to reveal any correlation between lipid content of the erythrocyte and permeability.

Hemoglobin, the red pigment of the erythrocytes, gives them their property of carrying oxygen and of aiding in carbon dioxide transport and is therefore of great physiological importance.

Hemolysis. Hemolysis is the act of discharging the hemoglobin from the corpuscles so that it becomes free in the plasma or other medium surrounding the erythrocytes. The older physiologists termed the process laking and blood so treated was said to be laked. As indicated below, there are a number of ways of producing hemolysis, but since the exact structure of the erythrocyte is still unknown, the mechanism of hemolysis is imperfectly understood. Some of the methods have clinical significance, while others do not.

1. Alternate freezing and thawing causes hemolysis, probably by rupturing the stroma.

2. Lowering the osmotic pressure of the plasma causes hemolysis. This lowering may be accomplished by adding weak salt solution or water to the blood. What occurs in such cases is a passage of water into the corpuscle by osmosis through its semipermeable membrane, where-

upon the corpuscle swells. This results in stretching, or possibly mechanical rupture, of its membrane and hemoglobin runs out into the surrounding medium. The transparent stroma left is spoken of as a shadow, or ghost, corpuscle (Fig. 2). Solutions that cause hemolysis by osmosis are said to be *hypotonic.* Solutions into which erythrocytes may be placed without producing osmotic changes are said to be *isotonic.* Such solutions cause no alterations in the size of the corpuscles. Solutions that exert a higher osmotic pressure than blood plasma are said to be *hypertonic.* They cause water to pass from the corpuscles by osmosis, and shrinking of the corpuscles results. Such erythrocytes are said to be crenated.

The isotonic solution which has been studied most and is of greatest interest is physiological salt solution, known also as physiological saline. It is an aqueous solution of sodium chloride and is usually prepared so as to contain 0.85 per cent of sodium chloride. This concentration of sodium chloride in water is satisfactory for practical use in mammals wherever an isotonic solution of sodium chloride is required. However recent studies (Aldred) by the vapor-pressure method indicate that the osmotic pressure of mammalian blood is somewhat higher than that of a solution containing 0.85 per cent of sodium chloride, and that interspecific differences of considerable magnitude exist. The accompanying table gives the average values. The values for the horse, cow, and hog are evidently nearly the same. The value for the goat is somewhat higher, and that for the sheep considerably higher, than the values for the other mammals.

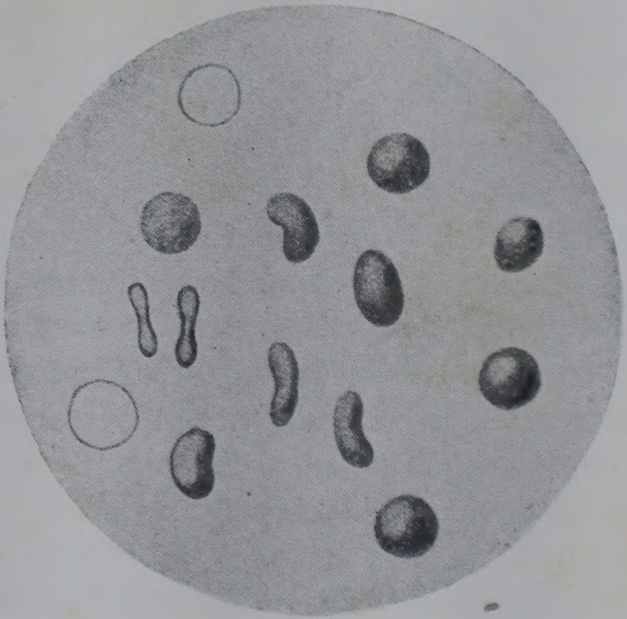

FIG. 2.—Various stages in the action of water on erythrocytes. Two shadow corpuscles are shown. (From Hawk and Bergeim's *Practical Physiological Chemistry,* Ed. 9, published by P. Blakiston's Son & Company, Inc.)

Osmotic Pressures of Blood

(Averages in equivalent concentrations of NaCl, grams per 100 gm. H_2O)

Sheep	0.978
Goat	0.955
Horse	0.927
Cow	0.936
Dog	0.933
Man	0.945
Woman	0.927

The osmotic pressure of the blood of birds is higher than that of the blood of mammals. In terms of equivalent concentrations of NaCl, the pigeon has an osmotic pressure of 1.004 and the hen 1.025. The frog, a cold-blooded animal, shows a value of 0.731, but the value for the tortoise is higher and very variable (0.80-1.16; av., 0.957).

While it is true that an 0.85 per cent solution of sodium chloride is approximately isotonic with mammalian blood plasma and that weak salt solutions when mixed with blood cause hemolysis, yet the extent to which the osmotic pressure of plasma can be lowered without causing hemolysis of all, or even any, corpuscles is considerable, and it varies somewhat among the different species. The point in terms of strength (per cent) of sodium chloride solution at which hemolysis just begins is called the *minimum resistance* of the erythrocytes. It indicates the resistance of the weakest corpuscles. The point at which all corpuscles are hemolyzed is termed the *maximum resistance*. It indicates the resistance of the strongest corpuscles. The figures in the accompanying table illustrate these values for various animals.

Resistance of Erythrocytes

Species	Minimum Resistance (av.)	Maximum Resistance (av.)	Author
	per cent NaCl	*per cent NaCl*	
Horse	0.57	0.42	Demmel
Ox................	0.59	0.42	Demmel
Sheep.............	0.69	0.46	Lyon
Pig...............	0.74	0.45	Lyon
Dog...............	0.46	0.33	Krumbhaar
Chicken...........	0.44	0.28	Demmel

It is not known that hemolysis caused by lowering the osmotic pressure of the plasma plays a part in the destruction of erythrocytes in the body under normal conditions. However, knowledge of this type of hemolysis is of practical importance in connection with solutions for intravenous injection. Nevertheless it is a fact that large amounts of water may be injected into the blood stream without producing any significant degree of hemolysis. In horses Roberts found that injections of over 4000 cc. of distilled water or tapwater regularly produced a temporary hemolysis and hemoglobinuria. No hemolysis was observed in any horse receiving less than 2000 cc. of distilled water or tapwater.

3. Stirring or agitating blood may cause hemolysis.

4. Blood submitted to high temperatures (over 50 degrees C.) undergoes hemolysis.

5. Substances that lower surface tension (saponin, soaps, bile salts) produce hemolysis. They probably combine with some constituent of the cell membrane or otherwise alter it. Alcohol, ether, chloroform, and acetone, which cause hemolysis, probably act similarly.

Hemagglutination. It has long been known that when blood serum or plasma of one animal is mixed with erythrocytes of an animal of another species, agglutination of the erythrocytes may occur. The process is spoken of as hemagglutination (heterohemagglutination). The active substance in the serum or plasma is designated as the agglutinin, whereas that in the erythrocyte is the agglutinogen. More recently it was discovered that agglutination of erythrocytes may occur when the serum or plasma and the erythrocytes of individuals of the same species are mixed. This reaction is known as isohemagglutination. It is especially important in human bloods, and must be taken into account in blood transfusions in humans. The blood of a person (donor) whose erythrocytes are agglutinated by the serum or plasma of a prospective recipient must not be transfused into that individual. Otherwise agglutination of the erythrocytes of the donor may occur in the blood stream of the recipient. Following agglutination, hemolysis may take place as a secondary effect. Agglutinins in the donor's plasma are relatively harmless, for they are greatly diluted by the blood of the recipient. Pooled plasma or serum is safe to transfuse into individuals of all blood groups partly for this same reason. Furthermore there is some neutralization of agglutinins within the pool. Isohemagglutinins are euglobulins.

Human bloods have been divided into several groups as regards the effect of the serum on other erythrocytes or the capacity of the erythrocytes to be affected by other serums. Definite blood groups have been less satisfactorily established in animals. The work of Little indicates that cattle fall into at least three groups as regards the presence of isohemagglutinins. In group I the serum is agglutinative, and the corpuscles are occasionally agglutinable. In group II the corpuscles are agglutinable, but the serum is not agglutinative. In group III the serum is not agglutinative and the corpuscles are not agglutinable. But irregularities in the reactions were noted. Amadon studied the question of isohemagglutination in a large number of samples of cattle blood by mixing on a glass slide a drop of plasma and a drop of a suspension of erythrocytes in physiological salt solution. The observations were made with the unaided eye. In no case was agglutination observed. Amadon is convinced that isohemagglutination is of no practical significance in blood transfusion in cattle. In horse blood, on the contrary, he found evidence of the existence of a number of types. "Horse blood should be typed previous to being used, to ascertain any possible incompatibility with that of the recipient." Amadon further noted "that ox plasma is universally and strongly agglutinative for horse cells, while horse plasma fails to clump ox cells as a rule, and when agglutination does occur it is a very weak reaction."

The recent work of Olson (**1940**) indicates that in dogs isohemagglutinins are present in blood plasma but not in the serum. Complete removal of fibrinogen from plasma removed the property of hemagglutination. Various reactions, some severe, some mild, followed the transfusion of blood whose incompatibility had been demonstrated in vitro. This investigator states, however, that in many cases, owing to the weakness of the natural isohemagglutinins in dogs, the transfusion of incompatible blood will produce no symptoms in this species. A division of dogs into blood groups is proposed by Olson.

The severe symptoms and death that may follow the transfusion of incompatible blood, especially in man, are due at least in part to the plugging of small vessels in vital organs by the clumps of corpuscles.

Blood groups and blood transfusion in animals are discussed in a recent article by Lager. References to the literature are given.

Origin of Erythrocytes. In the fetus the liver, spleen, and lymph nodes are the organs concerned in blood formation. In mammals throughout postnatal life the bone marrow is, under normal conditions, the only organ of erythropoiesis, as the process of formation of red blood corpuscles is termed (Jordan, **1942**; Osgood and Seaman). In birds the bone marrow is the main site of erythrocyte production, but the spleen forms erythrocytes to a small extent. Under certain pathological conditions in postnatal life the liver, spleen, and lymph nodes may assume again their fetal function of erythropoiesis.

Bone marrow is also the place of formation of granulocytes, it is an important seat of the production of platelets, and it is concerned to a small extent in the formation of lymphocytes. The production of these elements of the blood will be considered later.

In the bone marrow, erythropoiesis goes on continually, and corpuscles are poured into the blood stream at such a rate that the total number in the blood does not fluctuate greatly. According to one view the erythrocytes are formed extravascularly in the bone marrow. The entrance of the newly formed corpuscle into the capillary has been likened to the penetration, without rupture, of the film of a soap bubble by a needle; no stoma or opening is necessary. According to another view, erythrocytes develop intravascularly. There are, according to this theory, two kinds of capillaries in bone marrow: collapsed ones which are erythrogenic, and open ones through which blood flows. The young erythrocytes are forced into the blood stream by an opening up of the erythrogenic capillaries to the blood current. Recent studies of the cells of the bone marrow of dogs (Mulligan, 1941; Meyer and Bloom), newborn puppies (Mulligan, 1945), horses and cattle (Calhoun), and chicks before and after hatching (Burmester, Severens, and Roberts) have been made.

The normoblast (secondary erythroblast), the bone marrow cell which is the immediate forerunner of the erythrocyte, is nucleated, whereas the mammalian erythrocyte is not. The nucleus of the latter is lost by extrusion, or, according to some, by absorption, before the corpuscle enters the blood stream. In certain pathological conditions, however, nucleated forms may be found in the blood stream in great numbers.

In the blood of normal mammals there is constantly found a small percentage of erythrocytes that present a reticulated appearance when subjected to vital staining. These young forms are known as reticulocytes. They represent red cells that are discharged from the bone marrow before they are fully mature. They develop into adult erythrocytes in the blood stream. Their average amount in the blood of different species is as follows (Krumbhaar):

Reticulocytes of Blood (percentage of erythrocytes)

Man	0.3
Monkey	0.3
Dog	0.6
Cat	0.2
Guinea pig	3.0
Rabbit	2.0
Mouse	4.0

An increase in the reticulocytes of the blood (reticulocytosis) indicates that erythropoiesis is increased. Reticulocytosis occurs, for example, when the bone marrow in pernicious anemia is showing a favorable response to treatment.

The stimulus to erythropoiesis is not fully known. It is thought to be a lowering of the oxygen tension in the blood-forming organs. Another view is that some product of metabolism, probably carbon dioxide, may be concerned.

Erythrocyte-maturing Factor. In 1926 Minot and Murphy made the important observation that the feeding of liver to patients suffering from pernicious anemia is an effective treatment for this disease. Their studies were based on the earlier work of Whipple and collaborators in which it was shown that liver feeding is the best treatment for experimental anemia in dogs. Liver, as well as stomach, kidney, and other organs, contains a substance which has been shown to possess great potency in stimulating erythropoiesis. Its principal action is to cause maturation of the red cells and to prepare them for passage into the blood stream. On this account it is termed the *erythrocyte-maturing factor*. In pernicious anemia this substance is lacking and red cell maturation is largely inhibited at the megaloblast stage. There occurs a megaloblastic hyperplasia of the bone marrow, and the megaloblasts give rise to typical hyperchromic macrocytic erythrocytes, which pass into the blood stream in great numbers. Because the erythrocyte-maturing factor is effective in the treatment of pernicious anemia, it is known also as the *antianemic principle*. Apparently hemoglobin formation is not directly affected by an absence of the erythrocyte-maturing factor.

The erythrocyte-maturing factor is formed in the small intestine by the interaction of an *extrinsic factor* present in the food and an *intrinsic factor* produced by the cells of the pyloric region of the stomach and apparently also by the duodenal glands. It is absorbed from the intestine and stored mainly in the liver. The chemical composition of the erythrocyte-maturing factor is not yet known. For some time the evidence has indicated that it is a peptide, and recent work shows that a newly synthesized substance, pteroylglutamic acid, is in some way related to the erythrocyte-maturing factor. The new substance, also known as synthetic folic acid, gives favorable responses in pernicious anemia, but liver extracts apparently contain additional active factors since they give a greater response in pernicious anemia than is given by pteroylglutamic acid alone.

The extrinsic factor occurs in substances rich in the vitamin-B complex. Its chemical nature is not yet clear. It is soluble in water and is not destroyed by heating. The intrinsic factor is present in normal gastric juice and is presumably an enzyme.

The amount of the erythrocyte-maturing factor is not the same in the livers of all species. Horse liver ranks above pig liver, and beef liver below pig liver.

The erythrocyte-maturing factor is not effective in anemias due to iron deficiency, but it is effective in anemia due to hemorrhage.

Pernicious anemia has not been demonstrated to occur in animals.

The Fate of Erythrocytes; the Reticulo-Endothelial System. Erythrocytes are to be regarded as old cells when they have lost their nuclei. Therefore even before they begin their function of gas transport in the blood, they are entering upon their senility. The length of life of erythrocytes is not definitely known. Different methods yield different results. From Isaacs' review of the literature (1937) it is seen that the numerous estimates of the life of the mature erythrocyte vary from 4 to 120 days in different species.

Hawkins and Whipple have recently studied the question in healthy dogs with biliary fistula, in which animals there was a uniform output of bile pigment. The animals were then made anemic by bleeding or by blood destruction caused by injections of acetyl phenylhydrazine. Thereupon the blood-forming organs filled the circulation with a great mass of new erythrocytes and hemoglobin, and the elimination of bile pigment fell to low values for many weeks. In time, however, the output of bile pigment rose sharply. This marked the end of life of the new cells added to the blood as a result of hemorrhage or blood destruction. The time elapsing between the entrance of the new red cells into the circulation and their disintegration indicates the length of their life cycle in the experimental dogs. The following times were noted: 112, 120, 126, and 133 days. The average was 124 days.

Red blood corpuscles doubtless go to pieces by the hundreds of billions daily. The total number in the body of a horse is of the order of 300 trillion, and if the average life of these is assumed to be 100 days, then 3 trillion must be destroyed (and formed) in the body every day, or about 35 million every second.

The agencies of destruction of red blood corpuscles are the cells of the reticulo-endothelial system. These cells, known also as histiocytes or macrophages, vary in size, shape, and location, but they possess the common property of ingesting particulate matter brought into relationship with them. Reticulo-endothelial cells include the stellate or Kupffer cells found in the walls of the blood sinuses of the liver, the similar cells of the spleen, and certain cells of the bone marrow and lymph nodes. According to Rous's conception of erythrocyte destruction, the red corpuscles break up in the blood stream into smaller and smaller pieces still retaining their hemoglobin. When in a very fine state of division, these fragments are taken out by the cells of the reticulo-endothelial system by which the hemoglobin is doubtless split into its iron-containing, pigmentary part and its protein fraction. Then by a process that involves the splitting off and conservation of its iron-containing moiety, the pigmentary part is converted into the primary bile pigment bilirubin, which is an excretory product. By use of a radioactive isotope of iron ("marked" iron) it has been shown that iron derived from red cell destruction is readily and almost immediately utilized for new hemoglobin formation, even though ample reserves of iron are available in the organism (Cruz, Hahn, and Bale; Hahn, Bale, and Balfour). It has also been shown that when hemoglobin is destroyed the pigment radical is completely excreted as bile pigment whereas only 3 per cent of the released iron is excreted in the bile, the rest being conserved by the body. The liver and spleen are important storehouses of the conserved iron (Hawkins and Hahn).

Another way in which red corpuscles are destroyed is through phagocytosis by the cells of the reticulo-endothelial system. This method, probably of secondary importance in health, may be of great importance in disease.

Finally, there remains the possibility that erythrocytes are destroyed by hemolysis in the spleen and perhaps other places. But failure to find large amounts of free hemoglobin makes this view doubtful, at least as applied to the normal organism.

The relative importance of the reticulo-endothelial cells in different organs in the destruction of erythrocytes is not well understood. Variations are known to occur among the different species. In the dog Mann and co-workers have shown that the main seat of bilirubin formation is the red bone marrow. It is reasonable to suppose, therefore, that this is the principal place of erythrocyte destruction. In man the spleen is probably of great importance in the process; in the rabbit and guinea pig, less so; in birds the liver is the main seat (Krumbhaar). In most species of animals the liver is probably an important seat.

The Kupffer cells of the livers of ten species of laboratory animals were studied by Higgins and Murphey by making injections of suspensions of particulate matter (graphite) in the blood stream and studying its distribution in the liver. These investigators found that the distribution of the Kupffer cells in the cat is not so great as in the dog; that in the pig the cells appear to be less numerous than in any of the other animals studied; that in the guinea pig they are small and not numerous; that in the pocket gopher they are very numerous, etc.

The protein portion of the hemoglobin molecule is known as globin. It is a histone. Probably globin is used by the body in the formation of new hemoglobin. It will be recalled that stroma makes up some 6 to 8 per cent of the weight of the red corpuscle. What becomes of the constituents of the stroma when it disintegrates is uncertain. It is probable that they are added to the blood—the lipids and salts as such, the protein after hydrolysis to amino acids.

HEMOGLOBIN AND ITS COMPOUNDS AND DERIVATIVES

Hemoglobin, the pigment of the red blood corpuscles, is a compound that has been the inspiration for a vast amount of research. The recent writings of Barcroft and the older contribution of Gamgee help to summarize this work. Hemoglobin is a complex, iron-containing, conjugated protein composed of a pigment and a protein. The pigment is reduced heme and the protein is globin, a histone. These are combined to form blood hemoglobin (Anson and Mirsky). Heme is a ferrous-porphyrin pigmentary substance having the formula $C_{34}H_{32}O_4N_4FeOH$. It makes up 5 per cent of the hemoglobin molecule. Heme is widely distributed both in the animal and the plant kingdoms. This pigment is also known as hematin or protohematin. Reduced heme not only enters into combination with globin to form hemoglobin, as stated above, but it can also combine with many nitrogenous compounds to form hemochromogens. The combination between reduced heme and denatured globin is known as globin-hemochromogen. The combination between reduced heme and muscle globin is muscle hemoglobin or myohemoglobin. It is found in striated muscle. These relationships between reduced heme and other substances may be summarized as follows:

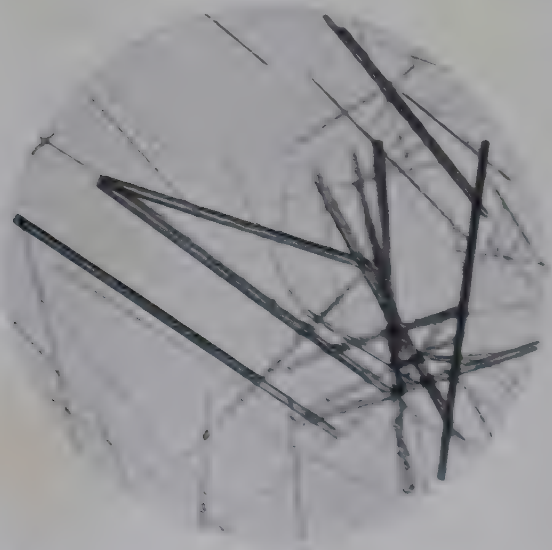

FIG. 3.—Oxyhemoglobin crystals of dog. (From *Publication No. 116*, Carnegie Institution of Washington.)

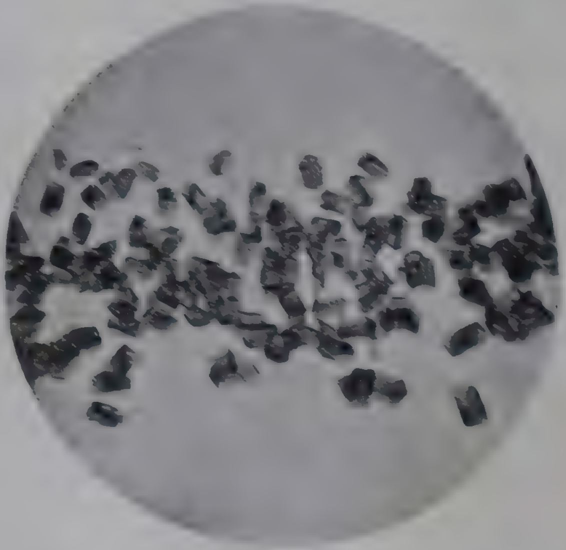

FIG. 4.—Oxyhemoglobin crystals of pig. (From *Publication No. 116*, Carnegie Institution of Washington.)

Reduced heme + globin → blood hemoglobin
Reduced heme + denatured globin → globin-hemochromogen
Reduced heme + muscle globin → muscle hemoglobin

There is reason to believe that most of the blood hemoglobin represents a polymerization of four molecules of the heme-globin combination. If this combination is represented by the conventional symbol Hb, then, according to this view, most of the blood hemoglobin would be Hb_4. Its molecular weight is approximately 65,000 (dog, 66,000; man, cat, pig, 65,000; rabbit, 69,000—McCarthy).

At least some of the pores of the glomerular membrane in the kidney are large enough to permit the hemoglobin molecule to pass through. Thus if hemoglobin is released in the blood stream, hemoglobinuria is likely to result.

Hemoglobins of Different Species. Hemoglobin is present in the blood of all mammals and of many animals far below the mammals. The hemoglobins are not identical compounds, however, even among the mammalian species. The differences are due to differences in the globin part of the molecule, for heme does not vary in composition either in the animal or the plant kingdom. Evidence that the hemoglobins in different animals are not identical is as follows: (1) The crystallography of the hemoglobins is not the same. This is shown by the extensive investigations of Reichert and Brown, who studied blood from over 100 species of animals. Hemoglobin from all species studied could be crystallized, usually as oxyhemoglobin, but the ease of crystallization, the shape and size of the crystals, and other factors varied greatly. The appearance of the crystals from several species of domestic animals is shown in Figs. 3 to 6. (2) The absorption spectra of the different hemoglobins are not identical. (3) The chemical composition of the globins is not the same, the differences being due apparently to differences in their amino acid content (Beach and co-workers).

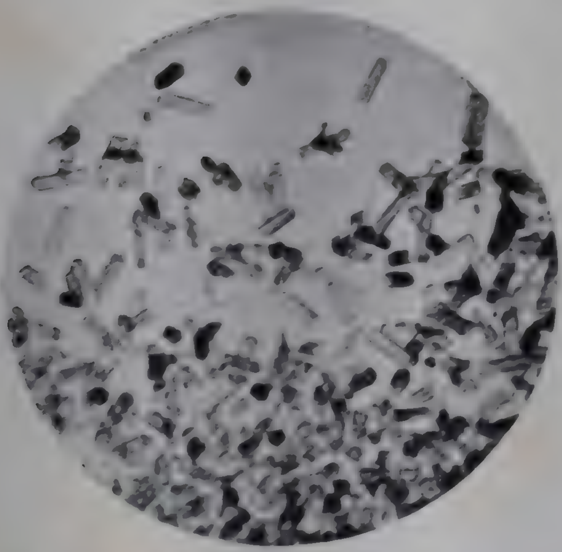

FIG. 5.—Oxyhemoglobin crystals of bullock. (From *Publication No. 116*, Carnegie Institution of Washington.)

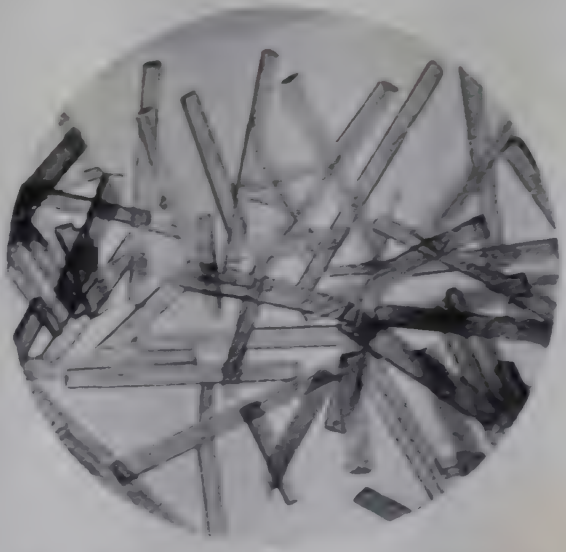

FIG. 6.—Oxyhemoglobin crystals of horse. (From *Publication No. 116*, Carnegie Institution of Washington.)

Characteristic species differences have been found in the molecular ratios of methionine to cystine.

Amount of Hemoglobin. The amount of hemoglobin in the blood is, in modern practice, usually expressed in grams per 100 cc. of blood.

HEMOGLOBIN CONTENT OF THE BLOOD

Species	Hb	Author
	gm. per 100 cc.	
Horse	11.3	Stewart and Holman
Cow	12.03	Miller
Sheep	11.18	Baker
Goat	10.9	Welsch
Pig	11.95	Oglesby, Hewitt, and Bergman
Dog	13.01	Mayerson
Cat	10.49	Landsberg (1940)
Rabbit	11.9	Fritsch
Turkey hen	10.5	Rhian, Wilson, and Moxon
Cock	13.5	Dukes and Schwarte
Hen	9.8	Dukes and Schwarte
Pigeon	15.34	Riddle and Braucher
Man	16.92	Williamson
Woman	15.53	Williamson

Throughout the class of mammals the hemoglobin range is about 10 to 16 grams per 100 cc. of blood. Average figures for man, the domestic mammals, and fowls are given in the table above.

Evidence has recently been obtained (Smith) that when the diet of the dog is adequate in all known blood-building factors, the hemoglobin content of the blood may be much higher (18 gm. per 100 cc. for adult dogs) than previous work has shown. Smith suggests that the lower values obtained in earlier investigations might have been due to inadequacy of the diets with respect to the B vitamins. It is pointed out, however, that the general health of dogs is nearly as good with hemoglobin values of 14 gm. per 100 cc. as with values of 18 gm.

The amount of hemoglobin in the blood is influenced by such factors as age, sex, season, the life habits of the species, and disease. Schwarte has reported a study of the variability of the hemoglobin content of the blood of pigs from birth to approximately 6 months of age. The effect of various changes in environment was noted.

Since the red blood corpuscles are the hemoglobin-bearing elements, one would expect to find in the normal animal a positive correlation between the number of these elements in the blood and the hemoglobin content. Such a relationship is illustrated, for dogs, in Fig. 7. In some types of anemia, however, this correlation does not hold.

The hemoglobin content of blood may be determined by instruments known as hemoglobinometers, and clinically the amount is sometimes expressed as a percentage of normal; but because the absolute amount of hemoglobin represented by 100 per cent on the scales of the different instruments varies greatly, it is advisable that all hemoglobin values be reported in grams per 100 cc., and that all hemoglobinometers be standardized by the same method. Some hemoglobinometers, including one form of the Newcomer instrument, give readings directly in grams per 100 cc. For hemoglobinometers yielding results in percentages of normal, a conversion to grams per 100 cc. may be made by multiplying the reading by the number of grams of hemoglobin per 100 cc. of blood represented by 100 on the scale of the instrument. Such figures for several instruments are: Haldane, 13.80; Oliver, 15.00; Tallqvist, 15.80; Sahli, 17.20.

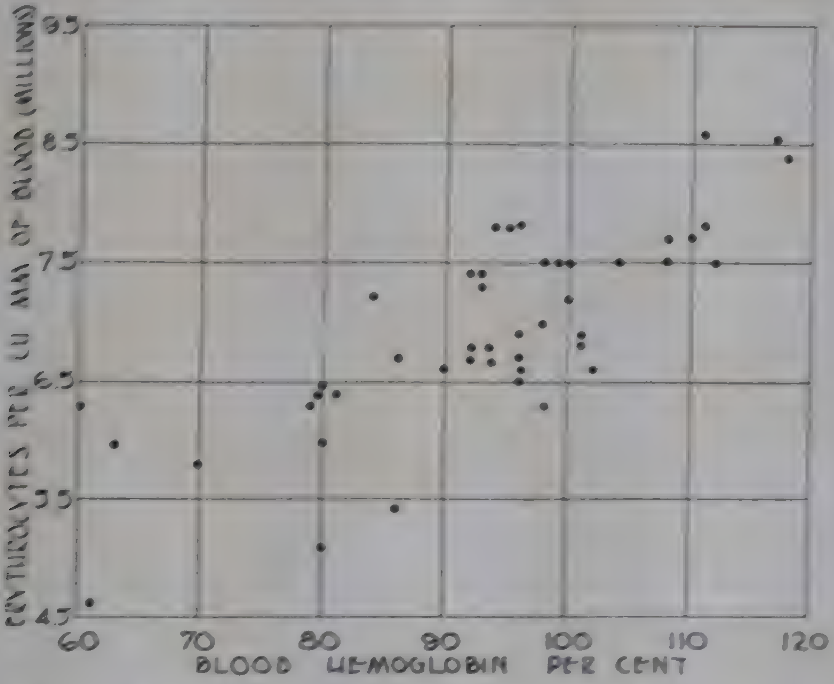

FIG. 7.—Showing the positive correlation between erythrocyte count and hemoglobin content of blood (dogs). (Data of Powers, Bowie, and Howard.)

Oxyhemoglobin. Hemoglobin, so-called reduced hemoglobin, has important physiological relationships with oxygen. (See also Chapter IX.) During the passage of the red corpuscles through the pulmonary capillaries, hemoglobin combines with oxygen to form oxyhemoglobin, which, as it traverses the systemic capillaries, loses its oxygen to the tissues and again becomes hemoglobin. Under appropriate conditions these reactions take place readily, and it is fortunate that this is so. Otherwise hemoglobin could not function as the respiratory pigment of the blood, for the red corpuscles, the hemoglobin carriers, spend only about one second traversing a capillary. The relation between hemoglobin and oxygen may be expressed in its simplest form as follows:

$$Hb + O_2 \rightleftarrows HbO_2.$$

However, it appears that what actually takes place in the body is more complex than this equation indicates, and is more accurately shown by the following equation:

$$Hb_4 + 4O_2 \rightleftarrows Hb_4O_8$$

in which Hb_4 represents the view, already stated, that most of the blood hemoglobin is made up of four molecules of the heme-globin combination. Since according to this conception the hemoglobin molecule contains four atoms of iron, it is evident that in oxyhemoglobin the ratio of Fe to O_2 is as 1:1. Hemoglobin owes its oxygen-carrying power to the pigment which it contains, and this in turn owes its oxygen-combining power to its iron content. The amount of iron in the blood is small, making up only 0.335 per cent of the hemoglobin molecule and 0.03 to 0.05 per cent of the blood itself. The body carefully conserves the iron resulting from hemoglobin destruction, only a small amount being lost daily. The dietary need for iron for hemoglobin formation is therefore small.

When saturated with oxygen, one gram of hemoglobin carries about 1.34 cc. of oxygen.

Oxyhemoglobin, its aqueous solutions, and arterial blood are bright red in color, whereas reduced hemoglobin, its aqueous solutions, and venous blood are purplish-red in color.

Muscle Hemoglobin (Myohemoglobin, Myoglobin). This pigment is found chiefly in those muscles that show slow, repetitive activity of considerable force (Millikan). The amount increases with age and activity. The pigment is a true hemoglobin, being composed of heme and globin. The heme of muscle hemoglobin is identical with that of blood hemoglobin, but the globins of the two pigments are slightly different. Muscle hemoglobin contains only one heme group, and hence only one iron atom, per molecule. Its molecular weight is approximately 17,000. The dissociation curve of muscle hemoglobin is hyperbolic, whereas that of blood hemoglobin is, under the conditions prevailing in the body, S-shaped (p. 220). The total amount of hemoglobin in striated muscles (dog) varies in different conditions from one-tenth to eight-tenths of that of the blood (Whipple). In beef cattle it has been shown that animals on pasture have a higher level of muscle hemoglobin than animals on dry lot. The differences could not be fully explained on a nutritional basis. The fact that the animals on pasture had more exercise was probably important (Shenk, Hall, and King).

Although muscle hemoglobin is doubtless concerned in muscle respiration, not a great deal is known about the physiology of this compound. When muscle contracts, its blood supply is temporarily interfered with because of compression of the minute blood vessels. Muscle hemoglobin might serve to yield a supply of oxygen to the contractile mechanism in spite of a discontinuous supply from the blood. Evidence indicates that it serves as a brief oxygen store in muscle. There is no evidence that it acts as a catalyst (Millikan).

In myohemoglobinuria ("azoturia") of horses, muscle hemoglobin appears in the urine.

Carbon Monoxide Hemoglobin. Hemoglobin has the power of combining not only with oxygen but also with certain other gases, for example, carbon monoxide. The compound carbon monoxide hemoglobin is a stable one, and when the gas is present in the respired air it combines with hemoglobin to the exclusion of oxygen. Carbon monoxide is therefore very poisonous, for to the extent that it occurs in the air it invalidates the hemoglobin of the blood as a carrier of oxygen. It also interferes with the giving up of oxygen to the tissues by the hemoglobin in the blood that is not combined with carbon monoxide. The carbon monoxide in combination with hemoglobin may be replaced by oxygen if the partial pressure of the latter is great enough. The replacement follows the law of mass action. Therapeutic measures in carbon monoxide poisoning are therefore directed toward increasing the partial pressure of oxygen in the blood. Oxygen inhalations are usually used. A mixture of oxygen and carbon dioxide may be administered, for carbon dioxide has a stimulating effect on the respiratory center. Injection of methylene blue has been recommended but it is of doubtful value.

Hemin. Hemin is the hydrochloride of heme. Its chemical constitution is known, and it has been synthesized. Hemin is easily prepared by heating together hemoglobin or dried blood, a grain of sodium chloride, and a drop or two of glacial acetic acid, on a glass slide. When so prepared, hemin usually assumes the form of brown rhombic crystals, readily seen under the microscope (Fig. 8). This test, known as the hemin test, is considered to be very reliable for blood.

Methemoglobin. Methemoglobin is a compound of hemoglobin and oxygen but, unlike the case of oxyhemoglobin, the union between them is strong. Methemoglobin is in reality the true oxide of hemoglobin, whereas oxyhemoglobin is an oxygenated derivative. It is a compound of oxidized heme (ferriheme, hematin) with globin. Methemoglobin is not ordinarily found in the blood stream in significant amounts because the oxygen of the air does not possess a high-enough oxidizing power to convert hemoglobin to methemoglobin.[3] Under some conditions, however, as after the administration of certain drugs (sodium nitrite, aminophenols), it may occur in the blood stream in varying amounts. To the extent that it is present, the blood loses its power to transport available oxygen to the tissues, for methemoglobin cannot act as a respiratory pigment because of the strong bonds uniting the hemoglobin and oxygen. Methemoglobin formed in the blood under these conditions gradually changes to oxyhemoglobin. When a sample of blood is exposed to the air for a long time, or hemoglobin is treated with potassium ferricyanide and many other substances, methemoglobin is formed. It occurs in the urine in certain pathological conditions.

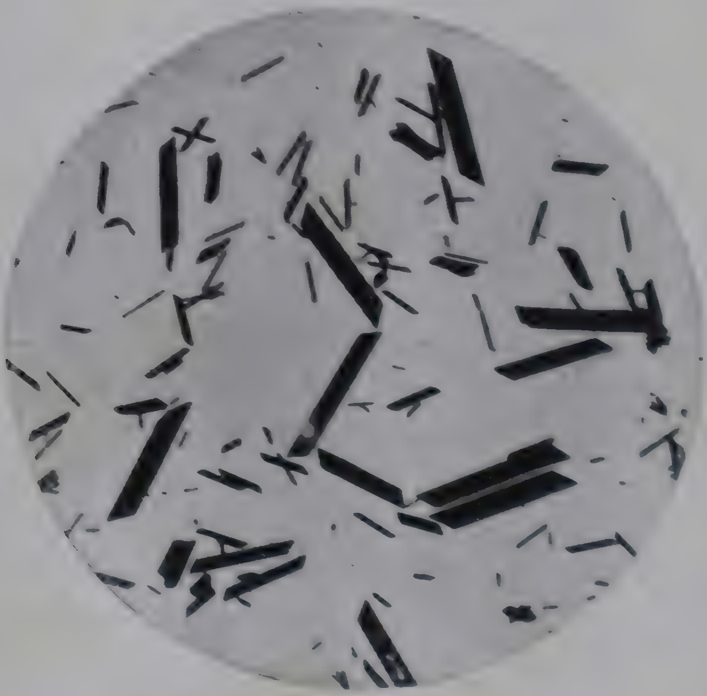

FIG. 8.—Hemin crystals prepared from sheep blood. (Reichert; from Hawk and Bergeim's *Practical Physiological Chemistry*, Ed. 9, published by P. Blakiston's Son and Company, Inc.)

Cytochrome. This is a widely distributed pigment found in both the animal and the plant kingdoms. In some animals, including mammals, it is present in the muscles together with muscle hemoglobin. It is composed of three different hemochromogens. Blood hemoglobin, muscle hemoglobin, and cytochrome may constitute a succession of oxygen carriers to the oxidative mechanisms of the cells. (See also p. 488.)

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[3] Recent work by Ramsay (1945) appears to show that horse blood may contain significant amounts of methemoglobin (ferrihemoglobin).

Hematoporphyrin. This is the name given to the iron-free pigment formed when hemoglobin or hemin is treated with a strong mineral acid. Hematoporphyrin is closely related chemically to the primary bile pigment bilirubin.

Absorption Spectra. When white light is made to pass through a solution of hemoglobin or one of its derivatives, certain wavelengths are absorbed. The resulting spectrum is termed an absorption spectrum; the regions of absorption are known as absorption bands. They may be revealed by examining the solution with a spectroscope. This is an instrument for producing and viewing the spectrum. In its simplest form, the direct-vision spectroscope, it consists essentially of a tube with an opening at one end and a convex lens at the other for producing a beam of light of parallel rays, a prism for resolving the light into its component parts, and a telescope for focusing. When white light is examined spectroscopically, a series of colors, known as the spectrum, is obtained. The colors are red, orange, yellow, green, blue, violet, and indigo. When sunlight is examined, certain fine, black, vertical lines are found at definite places in the spectrum. These are known as Fraunhofer's lines and are designated as A, B, C, D, E, etc. They are lacking in the spectrum of lamplight. The spectrum of a sodium flame shows a bright line in the yellow in the position of the D Fraunhofer line. Absorption bands of definite size, appearance, and position are given by solutions of hemoglobin and its derivatives in certain concentrations. Therefore spectroscopic examination serves to identify these pigments in solution.

Dilute oxyhemoglobin solutions when examined spectroscopically show two absorption bands between the D and E lines; the left band is narrower than the right (Fig. 9). Concentrated solutions show one band instead of two. When a reducing agent such as ammonium sulfide is added to dilute oxyhemoglobin solution, the two bands give place to a single band which begins just to the left of the D line and extends nearly to the E line. This is the spectrum of reduced hemoglobin (Fig. 9).

When carbon monoxide gas is passed through a dilute hemoglobin or oxyhemoglobin solution, carbon monoxide hemoglobin (carboxyhemoglobin) is formed. Its spectrum shows two absorption bands, which are similar in position and size to the bands given by oxyhemoglobin. However, it is easy to distinguish between the two compounds by adding a reducing agent. If the compound is carbon monoxide hemoglobin, the two absorption bands remain; if it is oxyhemoglobin, they

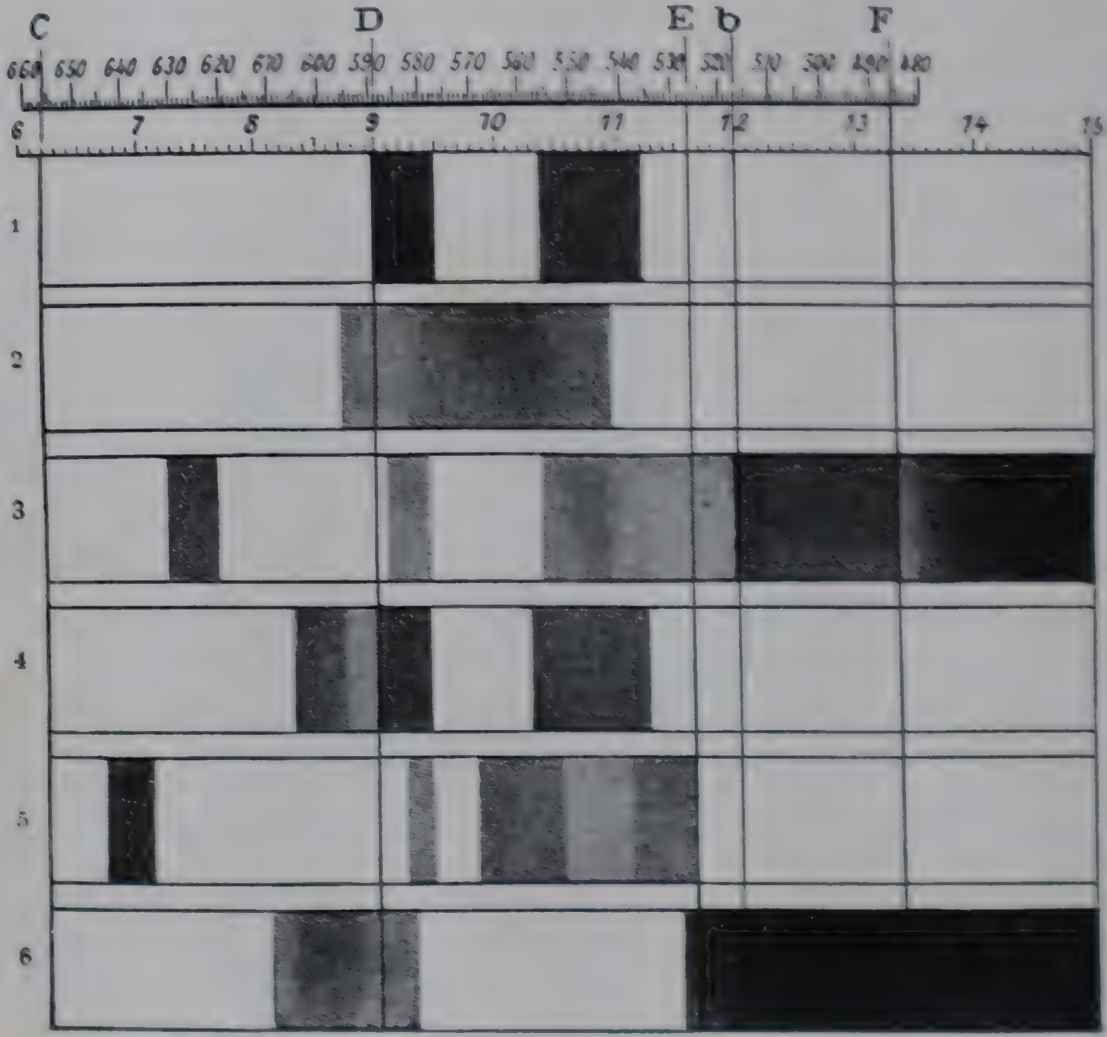

Fig. 9.—Absorption spectra of hemoglobin and some of its derivatives: 1, oxyhemoglobin, dilute solution; 2, reduced hemoglobin; 3, methemoglobin, neutral solution; 4, methemoglobin, alkaline solution; 5, hematin, acid solution; 6, hematin, alkaline solution. (Ziemke and Müller; from Howell's *Physiology*; copyright—W. B. Saunders Company.)

are replaced by one band. Carbon monoxide hemoglobin occurs in the blood stream in poisoning from carbon monoxide.

When a fairly strong solution of oxyhemoglobin is treated with potassium ferricyanide, chlorates, or nitrites, methemoglobin, in neutral solution, is formed. Its spectrum shows a distinct band in the red between the C and D lines and a somewhat narrower band just to the right of the D line. Still other bands are present (Fig. 9). The addition of a reducing agent causes the spectrum of oxyhemoglobin and then of hemoglobin to appear.

Hematoporphyrin in acid solution (prepared by adding undiluted blood to strong sulfuric acid) shows two bands that resemble somewhat the bands of oxyhemoglobin. However, careful examination serves to differentiate them.

WHITE BLOOD CORPUSCLES

White blood corpuscles, or leucocytes, are much less numerous than red blood corpuscles. They are of several kinds, and their physiology is incompletely understood. More work has been done on their function in disease than in health. Their cytology has been extensively studied in recent years (Bunting, Maximow, Cowdry).

Many classifications of white blood corpuscles have been proposed, but the differences are mainly in nomenclature. The following classification is in general satisfactory for the blood of most mammals:

- Leucocyte
  - Agranulocyte
    - Lymphocyte
    - Monocyte
  - Granulocyte
    - Neutrophile
    - Eosinophile
    - Basophile

Lymphocytes. These cells are relatively numerous in the blood of most species of domestic animals. They are usually about the size of an erythrocyte and have a large nucleus and a thin rim of cytoplasm. They are formed in lymphoid tissue (lymph nodes and nodules, spleen, etc.) generally and are in fact the main contituent of this tissue. They are believed to produce antibodies (Harris and co-workers) and to fix toxins. They are lost in large numbers from the body by migration to the intestinal and respiratory mucous membranes. They are not phagocytic (Bunting), that is, they do not possess the power of ingesting and digesting particulate matter, such as bacteria and tissue detritus, with which they come in contact. They show ameboid motility. Maximow states that there is little basis for a discussion of their functions and that it is not known whether they are active in the blood stream or in the tissues. Recent opinion holds that all leucocytes exert their main functions, not in the blood stream, but in the tissues. The blood is a means of transport of leucocytes.

Monocytes. These are the so-called transitional cells and the large mononuclear leucocytes. They occur in normal blood only to a limited extent. They are large and possess a single nucleus and a fairly abundant, faintly granular cytoplasm. Motility is well developed. Being actively phagocytic, they are able to ingest foreign particles of almost any sort. Their origin is probably from the cells of the reticulo-endothelial system.

Granulocytes. *Neutrophiles* are comparatively very numerous in the blood of man and most animals. They have an abundant, finely granular cytoplasm, the granules staining with neutral dyes. The nuclei vary much in outline, but frequently they are horseshoe-shaped. The number of lobes (connected by strands of nucleoplasm) into which the nucleus is divided forms the basis of a classification of neutrophiles. Determinations of this kind are known as Arneth counts. It is believed that the cells having the simpler nuclei are younger, whereas those having the more polymorphic nuclei are older. Arneth counts in certain pathological conditions are therefore thought to yield information about the degree of activity of the granulocyte-producing tissues. A preponderance of young forms would point to greater activity at the seat of production. In the normal blood of the horse, cow, and sheep it has been shown that single-lobed cells predominate. Fewer bilobed and trilobed forms are found (Simpson).

Neutrophiles are able to make ameboid movements, are actively phagocytic, and show rapid increases in number in pyogenic infections. They are formed in the red marrow of bones from extravascular neutrophilic myelocytes.

Eosinophiles are large cells containing numerous, large, acid-staining, cytoplasmic granules and a polymorphic nucleus. Their number in the normal blood of most animals is comparatively small. It is said that they are not ordinarily phagocytic. They are believed to originate from eosinophilic myelocytes of red bone marrow.

Basophiles have cytoplasmic granules that stain with alkaline dyes. They occur in normal blood only to a small extent. Their function is not known. Phagocytic power is slight or absent. They are believed to be different from mast-cells—so frequently found in the neighborhood of blood capillaries—though they resemble them histologically. Basophiles probably originate from basophilic myelocytes of the red marrow of bones.

Length of Life. Regarding the length of life of white blood corpuscles, there is little definite information. However, they are generally believed to be short-lived. Thus the life of neutrophiles is probably a matter of days or even just hours (Bunting). The average rate of disappearance of white blood corpuscles from the blood of leucopenic cats which were transfused with blood from normal cats was such that all of the white blood corpuscles could be replaced one and one-half times daily. This indicates an average length of life of about 16 hours (Lawrence, Ervin, and Wetrich).

The lymphocyte output of the thoracic duct has been found to be large enough to replace the lymphocyte content of the blood about five times daily.

The reticulo-endothelial cells of the liver and spleen are probably concerned in removing dead leucocytes or their fragments that escape autolysis (Bunting).

Number. White blood corpuscles are enumerated per cubic millimeter of blood. The table on p. 46 gives average numbers of white corpuscles and the relative proportions of the different classes in the blood of domestic animals (Kuhl, Welsch, Fritsch) and man. The number of leucocytes is subject to both physiological and pathological variations. The range of variation in the blood of normal dogs is shown in the accompanying graph (Fig. 10).

Recent extensive observations on the leucocyte picture of sheep have been made by Holman, and Venn has determined the leucocyte counts of pigs during the first twelve weeks of life.

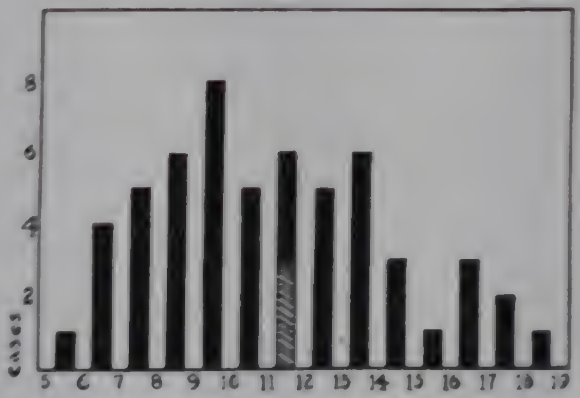

Fig. 10.—Average white corpuscle counts (thousands per cubic millimeter) in the blood of sixty normal dogs. (From Mayerson, *Anatomical Record*, published by the Wistar Institute.)

Pathological. An increase in the number of leucocytes is called leucocytosis, a decrease leucopenia. A few examples of pathological changes in the leucocyte count will be given. In equine influenza there is leucocytosis dominated by neutrocytosis. During convalescence lymphocytosis and monocytosis are generally observed (Maurer and Jones). Hog cholera is accompanied by leucopenia (Kernkamp). In the virus disease of cats known as panleucopenia there is a decrease in all the cellular elements of the blood. The greatest decrease, however, occurs in the leucocytes (Riser). Conner has made leucocyte counts and determined the Schilling indexes in a number of surgical conditions in horses. The Schilling index is the ratio of immature neutrophiles to mature. Changes of diagnostic and prognostic significance in the blood leucocyte picture have been observed by Dougherty in both experimentally produced and clinical cases of traumatic gastritis and traumatic pericarditis in cattle.

BLOOD PLATELETS

Blood platelets are oval, disklike particles only 2 to 4 microns in diameter. They are present in the blood of man to the extent of 200,000 to 300,000 per cubic millimeter. In young dogs Landsberg

(1939) found an average blood platelet count of approximately 155,000 per cubic millimeter. Most of the results fell in the range of 120,000 to 190,000. In the horse Stewart and Holman report a range of 110,000 to 300,000, with a mean of 176,000. Sopeña has made blood platelet counts in domestic animals. Platelets to a considerable extent rapidly disappear in drawn blood.

WHITE BLOOD CORPUSCLES

Species	Number	Percentage Distribution				
		Lymphocytes	Monocytes	Neutrophiles	Eosinophiles	Basophiles
	per cu.mm.	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Horse	10,300	38	4	54	4	<1
Ox	7,900	64	10	21	5	<1
Dog	12,600	25	8	57	10	<1
Sheep	7,440	48	6	42	4	<1
Goat	8,940	48	5	45	1.5	<1
Pig	17,110	47	8	41	2.5	<1
Rabbit	8,910	63	1	31	2	2
Cock*		40	2	49	5	3
Hen*		64	5	23	5	2
Pigeon		58	3	35.5	1.5	2
Man	5,500	23	7	67	3	<1

* Olson (1937) gives the average total leucocyte count in adult chickens as 19,800 per cubic millimeter. No sex differences in the leucocyte count were found.

There are several views regarding the origin of blood platelets. A widely accepted view (Sabin, 1922; Bunting) is that they are particles of protoplasm which arise as fragments from the giant cells of bone marrow. These cells throw out long protoplasmic projections which, penetrating the blood sinuses of the bone marrow, fragment into platelets. The latter are then carried away with the blood current. That this process accounts for all the platelets formed is doubted by a number of workers. It does not seem to occur on a large-enough scale. Work by Howell and Donahue suggests that the lungs are important sources of platelets. They found that systemic arterial blood (cats) contains a larger number of platelets than systemic venous blood. The conclusion was drawn that the new platelets are added to the blood as it passes through the lung capillaries and that there is a corresponding destruction of platelets as the blood passes through the systemic capillaries. Histological examination of the lungs showed the presence of giant cells in the lungs. This supports the view that the lungs produce platelets.

Platelets play a part in the coagulation of blood (p. 55).

Their number is diminished in the clinical condition known as purpura hemorrhagica. It has been claimed that platelets are related to *thrombocytes,* a class of nucleated cells found in the blood of birds and other submammalian forms; but this is doubtful. In adult chickens Olson (1937) found an average of 25,700 thrombocytes per cubic millimeter of blood.

THE SPLEEN

The spleen is the largest lymphoid organ in the body. However, its histology is more complex than that of lymphoid tissue generally. It has been compared histologically to a large hemolymph node. Many kinds of cells are found in the splenic pulp: reticulo-endothelial cells, splenocytes or pulp cells, and practically all kinds of blood cells. The spleen is abundantly supplied with blood, the course of which through the organ is peculiar. Capillaries are lacking in the ordinary sense, and blood passes right into the splenic pulp. It is then collected by the venous sinuses, which are drained by veins whose union leads to the formation of the splenic vein. The recent work of MacKenzie and collaborators supports this view that the open type of circulation is present in the spleen. They studied by transillumination the living spleen in five species of small mammals.

Functions. The functions of the spleen are not fully understood, although many facts of importance are known. That the organ is not necessary for life is well established. Splenectomy has been successfully performed not only on the small animals but also on horses, cattle, sheep, goats, and pigs (Quinlan, De Kock, and Marais). When the spleen is extirpated, other organs soon take over its functions or other adjustments are made, so that little or no disturbance of health ordinarily results. Craige noted anemia in a cow following splenectomy. Erythrocyte count, erythrocyte percentage volume, and hemoglobin content of the blood all showed a decrease. The following summary of splenic function is based in part on the comprehensive review of Krumbhaar (1926).

1. The spleen is an important reservoir for blood, which may be called upon under certain conditions, as during exercise, following hemorrhage, in carbon monoxide poisoning, during the administration of certain anesthetics (chloroform, ether), and in emotional states. The spleen undergoes at least two kinds of rhythmic changes in size. One of these is a slow expansion and contraction; the other, a frequently recurring systole and diastole. These movements are probably related to its function as a blood reservoir. In giving up blood in the conditions just mentioned the spleen undergoes strong contraction accompanied by vasoconstriction. In some species (horse, dog, cat) the blood coming from the spleen during this contraction is richer in corpuscles than the

blood of the general circulation, whereas in others splenic contraction augments only the blood volume. In animals of the first class the spleen must be able to concentrate blood coming to it by squeezing out plasma.

It is doubtful that the spleen of the fowl serves as a blood reservoir (Sturkie), and some recent work on the dog fails to support current opinion that the spleen has an erythrocyte-storing function in the normal dog. Evidently the subject of the reservoir function of the spleen is more complicated than was formerly thought, and further work will be required before knowledge in this field can be considered to be stabilized.

2. In the fetus the spleen is concerned in blood cell formation. In the adult it continues to form lymphocytes, monocytes, and possibly other cells, and its fetal activity of erythropoiesis can be resumed under certain pathological conditions.

3. It is concerned in the destruction of red blood corpuscles. This is by virtue of its high content of reticulo-endothelial cells and its power of making red blood corpuscles more susceptible to hemolysis, that is, more fragile. It has a very high iron content.

4. By reason of its reticulo-endothelial cells it is believed to be concerned in antibody formation, and because of the presence of numerous lymphocytes it plays a part in the resistance of the body to certain infections.

5. The spleen is of importance in the formation of bile pigment, the storage of iron, and possibly other phases of metabolism.

COMPOSITION OF BLOOD PLASMA

Samples of plasma may be obtained from drawn blood in which coagulation has been prevented. Chemical analyses and other studies reveal that the composition of blood plasma is extremely complex, and this is to be expected when the varied functions of blood, of which plasma forms 60 to 70 volumes per cent, are recalled. As would be expected, there is much similarity in the chemical composition of blood plasma in the different mammals. Nevertheless, important quantitative differences have been revealed. Following is a list of the best-known constituents.

Water	
Gases	Oxygen Carbon dioxide Nitrogen
Proteins	Albumin Globulin Fibrinogen

- Glucose
- Lipids
  - Fats
  - Lecithin
  - Cholesterol
- Nonprotein nitrogenous substances
  - Amino acids
  - Urea
  - Uric acid
  - Creatine
  - Creatinine
  - Ammonia salts, etc.
- Lactates
- Inorganic salts
  - Chlorides
  - Bicarbonates
  - Sulfates
  - Phosphates
  - of
    - Sodium
    - Potassium
    - Calcium
    - Magnesium
    - Iron

Mn, Co, Cu, Zn, I, etc. (small amounts or traces)
Enzymes, hormones, vitamins, pigments, etc.

QUANTITATIVE DATA ON BLOOD COMPOSITION

In the accompanying tables are shown the details of blood composition in several species of animals with respect to the most important constituents. The first three tables, from Abderhalden, are based on analyses made before modern methods of blood chemistry were devised; nevertheless they are regarded as being very reliable. Myers (1924) spoke of them as being "the most complete analyses which we possess on the blood of the various domestic animals, especially as regards the mineral constituents." The tables are still of more than historical interest.

In recent years many studies on the composition of the blood of animals, based on the newer methods, have appeared in the literature. The fourth of the accompanying tables represents an attempt to interpret, evaluate, and summarize some of these studies. It was prepared by Dr. C. E. Hayden and is founded on his own work and that of numerous other investigators.

PLASMA PROTEINS

Although the significance of several of the blood constituents has already been considered, a study of the significance of most of them will not be entered into in this chapter but will be deferred until such topics as respiration, absorption, metabolism, and the endocrine organs are treated. However, the plasma proteins may well be considered a this time.

Several proteins have been identified in blood plasma, albumin fibrinogen, and globulin, of which there are a number of fractions Classifications of the globulin fractions vary. According to one system the globulin fractions are euglobulin and pseudoglobulin I and II. I another classification, alpha, beta, and gamma globulins are recognized (Cohn). In an electrophoretic study of the blood plasmas fro twenty species of animals, including the domestic mammals and birds Deutsch and Goodloe concluded that distinct species differences i the mobility, amount, and number of the protein components occu In a given species, however, much greater constancy prevails. Th accompanying table, abstracted from a fuller one by Howe, give quantitative information concerning the plasma proteins in domesti animals. According to this author, "In man, sheep, goat, rabbit, dog guinea pig, and rat the albumins predominate over the globulins whereas in the horse, hog, and cow the relative proportions of these two classes of proteins are nearly equal or the globulins tend to be in excess of th albumins." In newborn animals (foals, kids, lambs, pigs) it has bee shown (Earle) that the euglobulin fraction of the plasma proteins i deficient and that pseudoglobulin I is present only in very smal amounts. Following the ingestion of colostrum these fractions sho large increases in the blood owing to their absorption from th colostrum. In this way, colostrum ingestion serves to increase the antibodies of the blood, for, as noted below, the antibodies are associate with the globulins. The absorption of globulins from colostrum ma have other beneficial effects on the newborn.

PLASMA PROTEINS

Animal	Total Protein	Fibrinogen	Albumin and Globulin
	gm. per 100 cc. of plasma	*gm. per 100 cc. of plasma*	*gm. per 100 cc. of plasma*
Cow	7.43	0.72	6.71
Horse			7.23
Horse	6.10	0.34	5.76
Sheep	5.74	0.36	5.38
Pig			6.38
Dog	6.06	0.58	5.48
Rabbit			5.53
Chicken			3.60

I. 1000 PARTS BY WEIGHT OF BLOOD CONTAIN

	Cow	Bull	Sheep 1	Sheep 2	Goat	Horse 1	Horse 2	Pig	Rabbit	Dog 1	Dog 2	Cat
Water	808.9	814.8	821.7	824.6	803.9	749.0	795.0	790.6	816.9	810.1	792.0	793.3
Total solids	191.1	185.2	178.3	175.5	196.1	251.0	205.0	209.4	183.1	190.0	208.0	204.3
Hemoglobin	103.1	106.4	92.9	102.8	112.6	166.9	125.8	142.2	123.5	135.4	145.6	143.2
Albumin	69.80	61.79	70.85	58.66	69.72	69.7	62.70	46.61	25.02	39.68	36.41	44.78
Sugar	0.7	0.68	0.732	0.708	0.829	0.526	0.900	0.686	1.026	1.09	0.72	0.851
Cholesterol	1.935	1.209	1.332	2.038	1.299	0.346	0.576	0.444	0.611	1.298	0.922	0.893
Lecithin	2.349	2.197	2.220	2.417	2.466	2.913	2.982	2.309	2.827	2.052	1.994	2.323
Fat	0.567	2.363	0.937	0.864	0.535	0.611	0.534	1.095	0.754	0.631	0.914	0.373
Fatty acids		0.495	0.488	0.490	0.395		0.387	0.473	0.307	0.739	0.684	0.782
Phosphoric acid as Nucleic acid	0.0267	0.0283	0.0285	0.0344	0.039	0.060	0.059	0.058	0.055	0.054	0.054	0.072
Soda	3.635	3.712	3.638	3.677	3.579	2.691	2.630	2.406	2.785	3.675	3.637	3.686
Potash	0.407	0.407	0.405	0.408	0.396	2.738	1.475	2.309	2.108	0.231	0.238	0.260
Ferric oxide	0.544	0.562	0.492	0.545	0.547	0.828	0.592	0.696	0.615	0.641	0.706	0.694
Lime	0.069	0.064	0.070	0.069	0.066	0.051	0.054	0.068	0.072	0.062	0.049	0.053
Magnesia	0.0356	0.030	0.033	0.033	0.040	0.064	0.066	0.089	0.037	0.032	0.034	0.039
Chlorine	3.079	3.081	3.080	3.091	2.923	2.783	2.384	2.690	2.898	2.935	2.908	2.815
Phosphoric acid in total ash	0.404	0.392	0.412	0.391	0.397	1.120	1.126	1.007	0.986	0.809	0.812	0.830
Inorganic phosphoric acid	0.171	0.174	0.190	0.145	0.142	0.806	0.807	0.749	0.685	0.576	0.588	0.555

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II. 1000 PARTS BY WEIGHT OF SERUM CONTAIN

	Cow	Bull	Sheep 1	Sheep 2	Goat	Horse 1	Horse 2	Pig	Rabbit	Dog 1	Dog 2	Cat
Water	913.6	913.4	917.4	916.8	907.7	902.1	915.1	917.6	925.6	924.0	923.0	926.9
Total solids	86.36	86.62	82.56	83.19	92.31	97.95	84.94	82.39	74.40	76.02	76.98	73.07
Albumin	72.5	69.73	67.50	68.40	78.07	84.24	70.82	67.74	53.57	60.14	61.12	58.60
Sugar	1.05	1.02	1.06	1.04	1.26	1.176	1.49	1.21	1.65	1.83	1.32	1.52
Cholesterol	1.238	0.901	0.879	1.309	1.070	0.298	0.521	0.409	0.547	0.709	0.658	0.600
Lecithin	1.675	1.869	1.709	1.599	1.727	1.720	1.746	1.426	1.760	1.699	1.755	1.716
Fat	0.926	3.542	1.352	1.262	0.624	1.300	0.834	1.956	1.193	1.051	1.642	0.788
Fatty acids		0.743	0.710	0.721	0.611		0.604	0.794	0.809	1.221	1.254	0.499
Phosphoric acid as Nucleic acid	0.0133	0.0134	0.0106	0.0161	0.018	0.020	0.015	0.0218	0.025	0.016	0.017	0.016
Soda	4.312	4.316	4.303	4.285	4.326	4.434	4.358	4.251	4.442	4.263	4.293	4.439
Potash	0.255	0.262	0.256	0.254	0.246	0.263	0.254	0.270	0.259	0.226	0.259	0.262
Ferric oxide												
Lime	0.119	0.111	0.117	0.131	0.121	0.111	0.111	0.122	0.116	0.113	0.111	0.110
Magnesia	0.045	0.042	0.041	0.041	0.041	0.045	0.046	0.041	0.046	0.040	0.046	0.043
Chlorine	3.69	3.686	3.711	3.697	3.691	3.726	3.655	3.627	3.883	4.023	4.138	4.170
Phosphoric acid in ash	0.244	0.235	0.232	0.240	0.237	0.240	0.242	0.197	0.242	0.242	0.250	0.236
Inorganic phosphoric acid	0.085	0.062	0.073	0.085	0.070	0.071	0.076	0.052	0.064	0.080	0.082	0.071

III. 1000 PARTS BY WEIGHT OF BLOOD CORPUSCLES CONTAIN

	Cow	Bull	Sheep 1	Sheep 2	Goat	Horse 1	Horse 2	Pig	Rabbit	Dog 1	Dog 2	Cat
Water........	591.86	618.63	604.79	627.78	608.72	613.15	613.20	625.61	633.53	644.26	627.16	624.17
Total solids....	408.14	381.39	395.23	372.24	391.30	386.84	386.82	374.38	366.48	355.75	372.85	375.82
Hemoglobin....	316.74	318.27	303.29	322.05	324.02	315.08	316.31	326.82	331.90	327.52	328.81	329.95
Albumin......	64.20	46.00	78.45	37.90	54.03	56.78	50.41	19.19	12.22	9.918	5.32	26.77
Sugar.........												
Cholesterol....	3.379	1.824	2.360	3.593	1.730	0.388	0.661	0.489	0.720	2.155	1.255	1.281
Lecithin.......	3.748	2.850	3.379	4.163	3.856	3.973	4.855	3.456	4.627	2.568	2.296	3.119
Fat...........												
Fatty acids....							0.0603	0.062		0.088		
Phosphoric acid as Nucleic acid	0.0546	0.0580	0.069	0.0736	0.0806	0.095	0.125	0.1045	0.107	0.110	0.101	0.145
Soda.........	2.232	2.509	2.135	2.380	2.174					2.821	2.856	2.705
Potash........	0.722	0.696	0.744	0.739	0.679	4.935	3.326	4.957	5.229	0.289	0.257	0.258
Ferric oxide....	1.671	1.681	1.606	1.707	1.575	1.563	1.188	1.599	1.652	1.573	1.594	1.599
Lime.........												
Magnesia......	0.0172	0.026	0.016	0.0187	0.0403	0.0809	0.098	0.150	0.077	0.071	0.065	0.0806
Chlorine......	1.813	1.878	1.651	1.801	1.480	1.949	0.460	1.475	1.236	1.352	1.361	1.048
Phosphoric acid in total ash..	0.735	0.705	0.822	0.714	0.699	1.901	2.466	2.058	2.244	1.635	1.519	1.605
Inorganic phosphoric acid...	0.350	0.397	0.455	0.275	0.279	1.458	1.916	1.653	1.733	1.298	1.214	1.186

USUAL NORMAL RANGE OF SOME CHEMICAL CONSTITUENTS OF THE BLOOD OF DOMESTIC ANIMALS

	Whole Blood (mg. per 100 cc.)								Serum (mg. per 100 cc.)		
	Sugar	Total non-protein nitrogen	Urea nitrogen	Uric acid	Pre-formed creatinine	Amino acid nitrogen	Lactic acid	Chlorides (as NaCl)	Total choles-terol	Calcium	Inorganic phosphorus
Cow	40–60	20–40	6–27	0.05–2.08	1–2.07	4–8.5	5–20	440–550	50–230	9–12	2.3–9.6
Sheep	40–65	20–38	8–20	0.05–1.93	1.2–1.93	4.6–8	9–12	460–528	—	9–12	2.5–9
Goat	43–65	30–44	13–28	0.33–1.0	0.9–1.82	—	—	429–528	55–200	9–12	3–11
Pig	40–250	20–45	8–24	0.05–1.95	1–2.7	8–8.5	—	440–590	152–154	9–15	4–11
Horse	60–110	20–40	10–20	0.90–1.09	1.2–1.9	5–7	10–16	440–500	—	9–15	2.4–4
Dog	70–100	17–38	10–20	0.0–0.5	1–1.7	6.7–8.5	8–20	430–550	125–250	9–11	2.2–4
Chicken (laying)	130–290	20–35	0.4–1.2	1.17–7.08	0.69–1.12	3.8–9	20–98	460–485	58–94	17–39	6–10
Chicken (nonlaying)	130–260	23–36	0.4–1.2	1.68–2.16	0.91–1.21	5.4–9.6	47–56	470–473	23–121	9–12	4–8
Turkey (nonlaying)	175–210	35–49	3.51–3.89	3.41–5.19	0.86–0.94	7.4–8.7	—	428–490	—	10–12	3.3–4.7

The reason why newborn animals of certain species lack globulins and therefore antibodies in the blood is that the placenta in these species is not permeable to these substances.

Origin. Much evidence favors the view that the plasma proteins are formed in the liver (Madden and Whipple; Mann). Thus as regards fibrinogen, when the blood in the portal vein is diverted around the liver directly into the posterior vena cava by experimental anastomosis of these veins (Eck fistula), or when the liver is removed or is poisoned or otherwise injured, the concentration of this protein in the blood is reduced. Although it is probable that the liver is the chief source of plasma protein, there is evidence that globulin, or some of the globulin fractions, originate extrahepatically (Berryman, Bollman, and Mann; Sabin, 1940). Recent work points to lymph nodes as a source of antibody globulin (Cope and Rosenfeld).

Functions. The function of fibrinogen is better understood than are the functions of the other plasma proteins. When fibrinogen is converted into fibrin, the latter constitutes the essential part of the blood clot, within the meshes of which the red corpuscles are entrapped. Following are other functions of the plasma proteins: (1) The older view was that the plasma proteins furnished the protein requirements of the tissues; but with increasing knowledge of amino acid metabolism this view was largely discarded. There is recent evidence (Madden and Whipple) that the earlier view may be correct, at least in an emergency such as fasting. (2) They contribute to the viscosity of the blood and thus aid in maintaining normal blood pressure. (3) They exert a low but constant osmotic pressure in the blood. Because they are colloidal and therefore nondiffusible, this osmotic pressure opposes the blood pressure in the capillaries and thus prevents undue passage of fluid into the tissues. The albumins account for nearly 80 per cent of the colloid osmotic activity of the plasma. (4) They influence the suspension stability of the blood (p. 23). (5) The antibodies of the blood appear to be definitely associated with the globulins; they can be separated from the blood in the gamma-globulin fraction. Some regard them as being, in fact, modified plasma globulins.

COAGULATION OF BLOOD

The ability of the blood to clot or coagulate when drawn from the blood vessels is essentially a process of the plasma and is one of its most important properties. The physiological value of coagulation lies in the fact that it serves to seal injured blood vessels and thus to stop hemorrhage. The gross physical changes undergone by blood during clotting have long been recognized and are easily followed. At first the blood is perfectly fluid but soon becomes thicker and finally reaches the consistency of soft jelly. This soft mass gradually becomes firmer owing to shrinkage of the fibrin framework of the clot, and in shrinking there is pressed out of the clot a clear, watery fluid termed blood serum. This closely resembles blood plasma but differs from it somewhat in composition. In the clot the fibrin is deposited in the form of densely packed needles of ultramicroscopic size and crystalline appearance (Fig. 11). The fibrin needles are strengthened at their intersections by knots of intact platelets deposited there after the fibrin is laid down. In this way the platelets assist in making the clot firmer and more elastic. Clots formed in the absence of platelets lack firmness and shew less contractility (Tocantins).

In the spaces of the fibrin network the red corpuscles are entangled. White corpuscles are also present to some extent, but, owing to their powers of ameboid movement, they may migrate into the serum above. As a blood with rapidly settling erythrocytes undergoes coagulation, the upper part of the clot takes on a yellowish appearance and is known as the buffy coat. This part is composed principally of coagulated plasma, the corpuscles having largely settled out. It is often well defined in coagulated horse blood.

The chemical or physicochemical changes occurring during clotting are complex, as researches have disclosed. There is still much difference of opinion as to the exact nature of some of these processes, although certain conceptions regarding the chemistry of clotting are widely accepted. It is generally recognized that fibrin, the essential part of the clot, is formed from the blood protein fibrinogen. Further, it is widely believed that the change of fibrinogen to fibrin is brought about by the action of a substance, not normally present in blood but formed when blood is shed, to which the name thrombin is usually applied. The source of thrombin is an inactive substance in the blood, prothrombin, which is quickly activated when blood is shed. Recent evidence indicates that thrombin and its precursor prothrombin are carbohydrate-containing proteins (Seegers). Prothrombin is a plasma protein fraction.

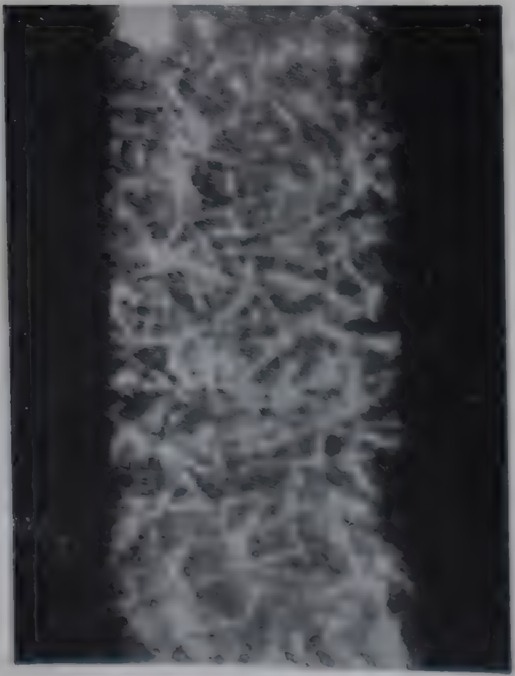

Fig. 11.—Fibrin needles as seen with the ultramicroscope. Plasma of oxalated dog's blood was clotted by thrombin. (From Howell's Physiology; copyright, W. B. Saunders Company.)

It is formed in the liver. Vitamin K is necessary for its production, but the way in which it acts in the formation of prothrombin is still unknown. Quick (1941) has shown that the level of prothrombin in the plasma varies greatly in different species. Designating the plasma prothrombin level of the rabbit as 100, that of the dog is 100; cat, 60; horse, 40; man, 20; cow, 16.

The manner of conversion of prothrombin to thrombin is variously explained, although calcium ions are recognized as playing a necessary part at this stage of clotting. According to one theory (Morawitz), calcium reacts with prothrombin in the presence of a substance, formed particularly from injured body cells and the disintegration of blood platelets, called thrombokinase or thromboplastin. A product of the interaction of these three substances is thrombin. The changes occurring during coagulation according to this view may be summarized as follows:

Blood platelets, tissue cells = thromboplastin
Thromboplastin + Ca + prothrombin = thrombin
Fibrinogen + thrombin = fibrin

Howell, on the basis of his researches, held that calcium ions alone are capable of converting prothrombin to thrombin. This reaction is normally prevented in the blood vessels because prothrombin is inactivated or bound by a substance called antiprothrombin. According to Howell, antiprothrombin is the same as heparin.

In Howell's theory of blood coagulation the action of thromboplastin is to break up the prothrombin-antiprothrombin combination and thus to release prothrombin. The latter substance then reacts with calcium ions to form active thrombin. Howell considered thromboplastin to be comprised, to a large extent, of the phospholipid cephalin. Howell's theory may be summarized as follows:

Prothrombin-antiprothrombin (heparin) + thromboplastin (cephalin) = prothrombin
Prothrombin + Ca = thrombin
Thrombin + fibrinogen = fibrin

Recent evidence (Ferguson, 1943, 1946) reaffirms the view of Morawitz that a thromboplastic factor, as well as ionized calcium, is necessary for the conversion of prothrombin to thrombin. Furthermore it seems that the plasma itself is the main source of the thromboplastic factor. Ferguson believes that undue emphasis has been placed on the platelets and tissue cells as sources of thromboplastic substances.

Little or no free cephalin exists in blood plasma. It is postulated that an enzyme, serum tryptase, is concerned in the release of free cephalin in drawn blood. The enzyme is inactive in the blood stream because of the presence of a tryptase-inhibitor. When blood is shed, there occurs an upset in the stability of the colloidal state of the plasma and active tryptase is formed. This enzyme then catalyzes the interaction of prothrombin, cephalin, and calcium to form free thrombin. The latter reacts with fibrinogen to form free fibrin. More remote but very important actions of the enzyme tryptase are to cause retraction of the blood clot and finally resolution of the clot by fibrinolysis.

Heparin. This anticoagulant substance was prepared from liver in Howell's laboratory in 1916. Heparin is now available in purified form. It appears to be a polysaccharide of large molecular size containing nitrogen. It has been prepared from a number of tissues. The evidence indicates that it is produced by mast-cells (tissue basophiles). The anticoagulant action of heparin is complex and poorly understood. A modern suggestion is that it exerts its inhibitory action particularly on the thromboplastic reactions. It delays or prevents clotting in vivo or in vitro. Heparin injections may be used clinically to prevent thrombosis and embolism.

The anticoagulant powers of heparin, prepared in the form of its barium salt, are not the same in all species: dog, 10; ox, 5; pig, 2; sheep, 1. The chemical basis for the differences is not known (Jaques, Waters, and Charles).

Defibrinated Blood. If blood during the clotting process is whipped or stirred with a bundle of twigs or fine rods, or is shaken with glass beads, the fibrin will deposit as a spongy mass on the stirrer or as a shredded mass among the beads. Blood from which the fibrin has been so removed is known as defibrinated blood. It is composed of serum, erythrocytes, and leucocytes and resembles normal blood, although of course it cannot clot again. It went through the chemical changes of clotting while being stirred or shaken.

Coagulation Time. The time required for blood to coagulate varies widely in different species and somewhat even in animals of the same species. In all cases, marked variations can be induced by varying the conditions under which the blood is kept after being shed. Amendt gives coagulation times as shown in the table on the next page.

Factors that Hasten Clotting. Some of the ways by which clotting may be accelerated are as follows: (1) Increasing the contact with foreign matter, as by the use of gauze packs or tampons in surgical practice or shallow containers for drawn blood. Foreign surface is be-

AVERAGE COAGULATION TIME (MINUTES) AT 25° C. (BÜRKER'S METHOD)

Fowl	4½
Rabbit	4
Dog	2½
Pig	3½
Sheep	2½
Goat	2½
Ox	6½
Horse	11½
Man	5
Cat	1-3 (Hartman)

lieved to upset the stability of the colloidal state of the plasma and thus set up the thromboplastic reactions. (2) Increasing the temperature to which the blood is exposed. (3) Gently agitating the blood. (4) Increasing the concentration of calcium ions in drawn blood. Injections of calcium salts have not been very helpful. (5) Adding thrombin to the blood. In human surgical practice the checking of hemorrhage is being accomplished by the application to the bleeding area of fibrin foam, an absorbable tampon, prepared from human fibrinogen and thrombin (Cohn). (6) The application to the bleeding area of tissue extracts containing thromboplastic substances may be helpful. In veterinary medicine subcutaneous injections of such material are sometimes made. But there is some danger of anaphylactoid reactions.

Factors that Prevent Clotting. Clotting may be prevented in a number of ways, such as: (1) The addition of a soluble oxalate to the blood to the extent of about 0.2 per cent of the blood. This forms a nonionizable compound with calcium and may have other anticoagulant action. (2) The use of sodium fluoride in an amount sufficient to cause its concentration in the blood to be 0.2 to 0.3 per cent. It is believed that fluorides act similarly to oxalates, but it is possible that they also prevent the disintegration of the blood platelets. (3) The addition of sodium citrate to the blood. The precise way in which citrates act to prevent clotting is unknown. Forming a nondissociable compound with calcium is believed to be a part of their action. Oxalates and fluorides are too toxic for use in blood intended for intravenous injection. Sodium citrate in the amount usually used clinically is generally safe. However, Ivy and co-workers point out that when a large amount of citrated blood or citrated plasma is to be given, as after massive hemorrhage, the toxicity of the citrate must be considered. Their work on dogs indicates that a total dose of 1.5 gm. of sodium citrate per 10 pounds of body weight may be fatal. In some cases even smaller doses were lethal. The work of Roberts on horses suggests toxicity of the same order in this species. Sodium citrate in doses of 60 to 90 gm. intravenously produced severe physical symptoms. (4) Heparin may be used in vitro or in vivo to prevent or delay coagulation. It is apparently nontoxic. (5) Hirudin (from the leech) prevents or delays coagulation, possibly by inactivating thrombin. (6) Peptone injected into the blood stream prevents clotting, apparently by causing an increased production of heparin. However, peptone causes a severe fall in blood pressure and the development of a shocklike state.

Anions of high valency are believed to prevent coagulation by acting on thrombin; cations of high valency by affecting fibrinogen (Smith, 1942).

Sweet-Clover Disease. The feeding of spoiled or damaged sweet-clover hay or sweet-clover silage may cause the death of cattle or sheep from hemorrhage preceded by a gradual increase in the coagulation time of the blood. The disease usually ends in death due to hemorrhages into the tissues or from accidental or surgical wounds. The work of Roderick shows that the delayed coagulation is caused by a progressive decrease in the amount of prothrombin in the blood. The blood calcium level and the platelets are unaffected. Intravenous injection of freshly defibrinated blood from a normal animal usually results in recovery.

The hemorrhagic agent in improperly cured sweet-clover hay has been shown to be dicoumarin (Dicumarol), $C_{19}H_{12}O_6$. The synthetic product when fed to animals of various species will lower the prothrombin level and produce a hemorrhagic condition typical of sweet-clover disease (Stahmann, Huebner, and Link; Link). The evidence indicates that dicoumarin depresses the production of prothrombin by preventing the utilization of vitamin K by the liver. There is also evidence that the hypoprothrombinemia of dicoumarin poisoning can be relieved to some extent by feeding vitamin K. It is suggested that vitamin K might replace the toxin or that the liver cells undamaged by the toxin can make more prothrombin when an abundant supply of vitamin K is present (Quick, 1944).

A Bleeding Disease in Swine. A bleeding disease occurring in a strain of swine has been described by Hogan and co-workers, Bogart and Muhrer, and Mertz. The affected animals may bleed to death from slight wounds or from apparently spontaneous hemorrhages. The disease is much like the condition in man known as hemophilia. However, in swine both sexes have the defect and both transmit it, whereas in man hemophilia affects only males and is transmitted only through females. The whole-blood coagulation time and the saline bleeding time (the time required for hemorrhage to cease from a wound unmersed in physiological salt solution) are greatly prolonged. The blood platelets are normal in number but they disintegrate more slowly than normal. Capillary resistance, measured by a suction tube applied to the skin, is abnormally low, and there is evidence of other blood-vessel defects.

Hemophilia in Dogs. A bleeding disease in a family of dogs has been reported by Field, Rickard, and Hutt. The tendency to bleed appeared only in males and was transmitted as a sex-linked, recessive character. The coagulation time was greatly prolonged, but the bleeding time, clot-retraction time, prothrombin time, and platelet count were normal. The authors concluded that the condition was hemophilia. The deficiency in hemophilia appears to be that of thromboplastic substance.

BLOOD VOLUME

It is impossible to determine the volume of blood in the body merely by bleeding the animal to death, for much blood is left in the blood vessels even after the animal dies of hemorrhage. The blood vessels must therefore be washed out thoroughly and the amount of blood represented by the washings must be added to that removed by bleeding. This gives the total amount of blood in the body, which may be expressed as a percentage of body weight. Such is essentially the method of Welcker. It is also known as the direct, or wash-out, method. Some average results according to the work of this investigator and others are as follows (Reichert and Brown)[1]:

Blood Volume (percentage of body weight)

Horse	9.7
Bullock	7.7
Sheep	8.0
Goat	6.2
Dog	7.2
Cat	6.5
Rabbit	6.2
Birds	8.0

By an improved Welcker method Barlow and Biskind found the blood volume of pigeons to be 6.5 per cent of the body weight.

Numerous indirect or bloodless methods of estimating blood volume have been devised (Lamson and Nagayama, Rowntree and Brown, Erlanger). A dye method is commonly used. This involves the determination of the plasma volume by measuring colorimetrically the degree of dilution of a known amount of dye injected into the circulation.

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[1] See also Tigerstedt, vol. 4, and Erlanger.

To the plasma volume must be added the volume of the corpuscles, the percentage value of which is determined by means of the hematocrit.

The calculation may be made by use of the following formula:

$$\text{Blood volume} = \frac{\text{Plasma volume} \times 100}{\text{Plasma percentage}}.$$

A discussion and critique of blood-volume methods may be found in Wiggers' book.

Using a dye method in cattle, Miller obtained an average blood volume of approximately 6.7 per cent of body weight. Using the same method in sheep, Baker obtained an average value of approximately 6.8 per cent.

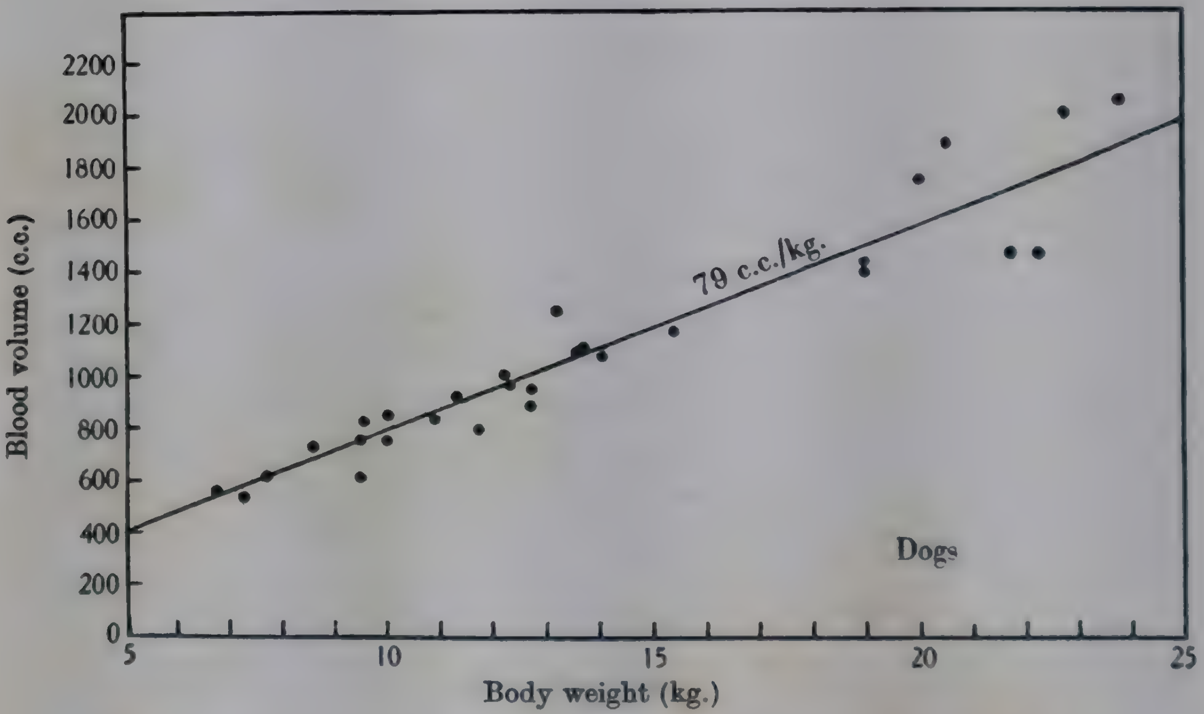

FIG. 12.—Relation between blood volume and body weight in dogs. (From Courtice, *Journal of Physiology*, 1943, 102.)

In growing dairy cattle Turner and Herman, using a dye method, found an average blood volume of 5.81 per cent of body weight; in nonlactating cows, 6.38 per cent; and in lactating cows, 8.11 per cent. The plasma values were 3.5, 3.78, and 4.92 per cent, respectively. By the "drain-out" method the average blood volume was found to be 4.13 per cent of body weight. This low value is explained by the fact that all the blood of the body cannot be recovered by the drain-out method; the heart stops while there is still a good deal of blood in the body.

By use of the blue dye T-1824, Courtice estimated the blood volume in a number of normal rabbits, dogs, goats, and horses. The mean values are respectively: plasma volumes, 50, 54, 53, and 51 cc. per kilogram of body weight; blood volumes, 70, 79, 70, and 72 cc. per kilogram. The blood volume in these animals, varying greatly in size, was found to be proportional to the body weight and not to the body surface area. The values for dogs and goats are shown in Figs. 12 and 13. Four highly trained greyhounds had much higher blood volumes due to greater cell volumes.

Using a dye method Pappenheimer and co-workers studied plasma and blood volumes in chicks ranging in age from 1 to 50 days. In normal chicks the average plasma volume was 5.5 cc. per 100 gm. of body weight; the average blood volume, 8.3 cc. per 100 gm. In chicks showing the disease known as nutritional encephalomalacia, plasma and blood volumes were not significantly affected.

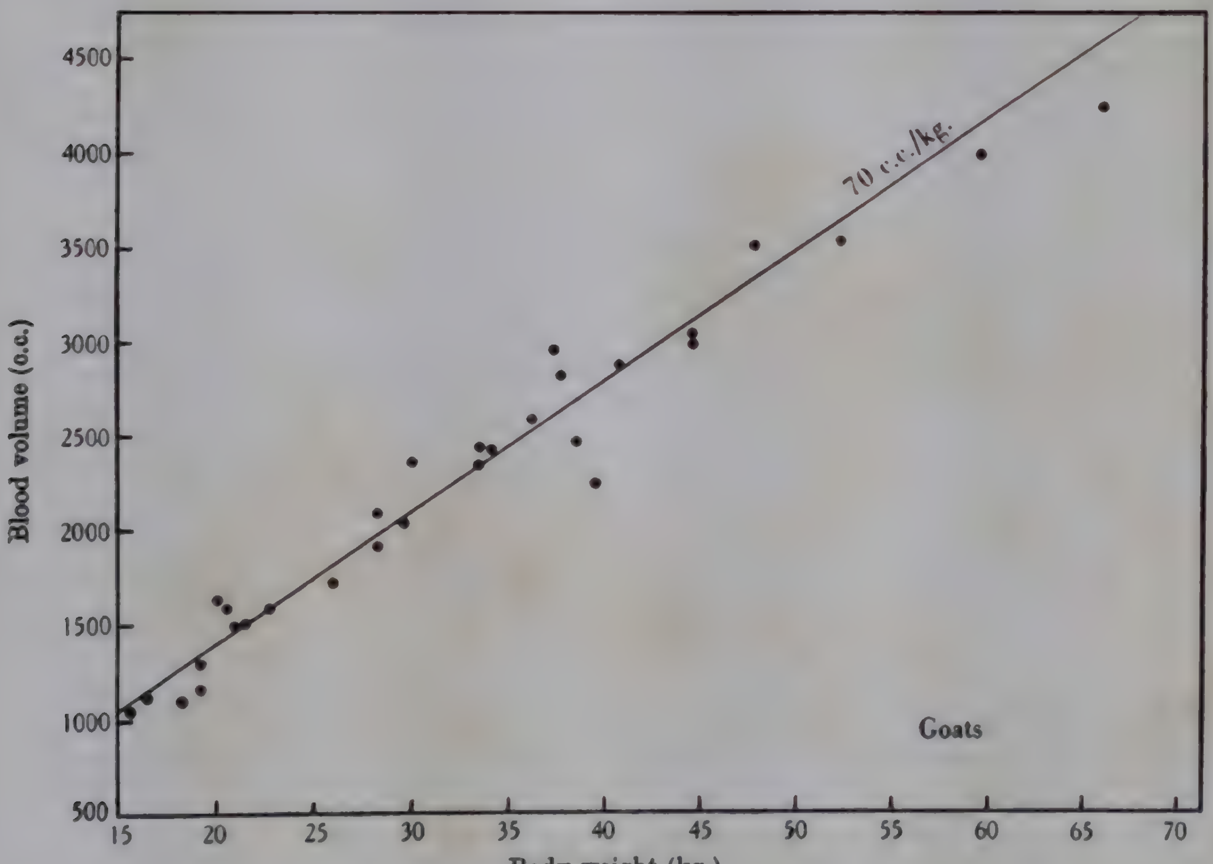

FIG. 13.—Relation between blood volume and body weight in goats. (From Courtice, *Journal of Physiology*, 1943, 102.)

The volumes of blood, plasma, and corpuscles per kilogram of body weight of lambs at different ages are shown in Fig. 14. The changes in the volume of blood, plasma, corpuscles, and other factors in a pregnant sheep are shown in Fig. 15.

Hahn has prepared a chart from which the red-cell mass of dogs can be estimated if the jugular hematocrit value and the body weight are known.

Blood Loss. Hemorrhage in dogs up to 2 per cent of body weight, or about 25 per cent of the total blood volume, usually causes no serious physiological effect (Meek and Eyster). Ivy and co-workers studied the effect of massive hemorrhage on dogs (local anesthesia) by inserting a glass cannula into the central (heart) end of a carotid artery and letting the animals bleed as much as they would. Bleeding ceased in 7 to 15 or 20 minutes. Under these conditions the dogs lost 45 to 67 per cent of their estimated total blood volume. Most of the dogs so treated (85 per cent) died unless the blood loss was replaced by injections of blood or blood substitutes. However it is a remarkable

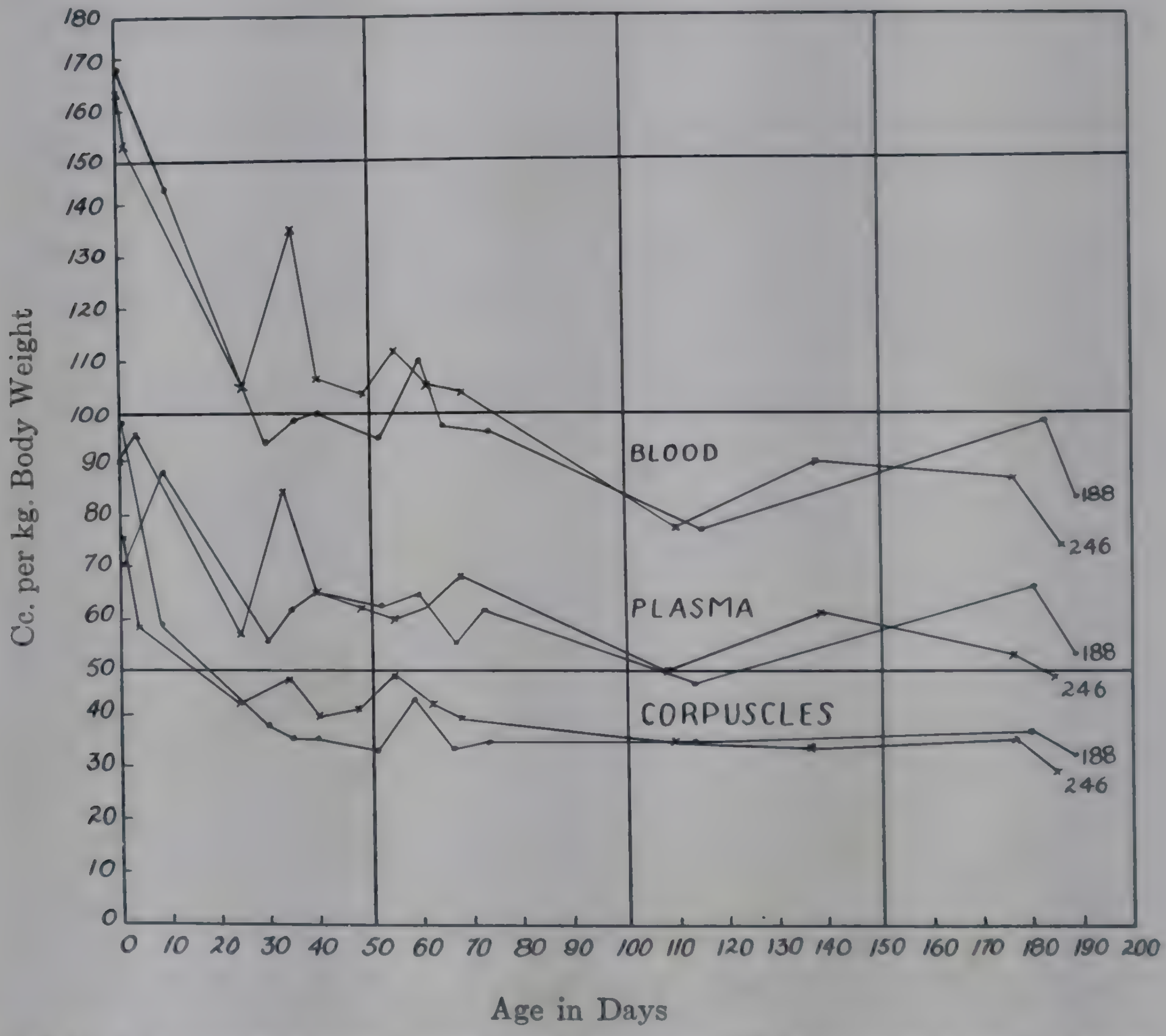

FIG. 14.—Volumes of blood, plasma, and corpuscles per kilogram of body weight at different ages. Lambs. Ordinates, cc./kg. body weight. Abscissa, age in days. Note that the fluctuations of the plasma are greater than those of the corpuscles. (Redrawn and slightly modified from Gotsev, *Journal of Physiology*, 1938–39, **94**.)

fact that 15 per cent of the dogs losing such large amounts of blood survived without transfusions. This means that an occasional dog can suffer a blood loss equal to two-thirds of the estimated blood volume and recover without transfusion.

The maximum degree of acute hemorrhage that the (anesthetized) rat can tolerate is about 3.5 per cent of body weight (Zweifach, Lowenstein, and Chambers).

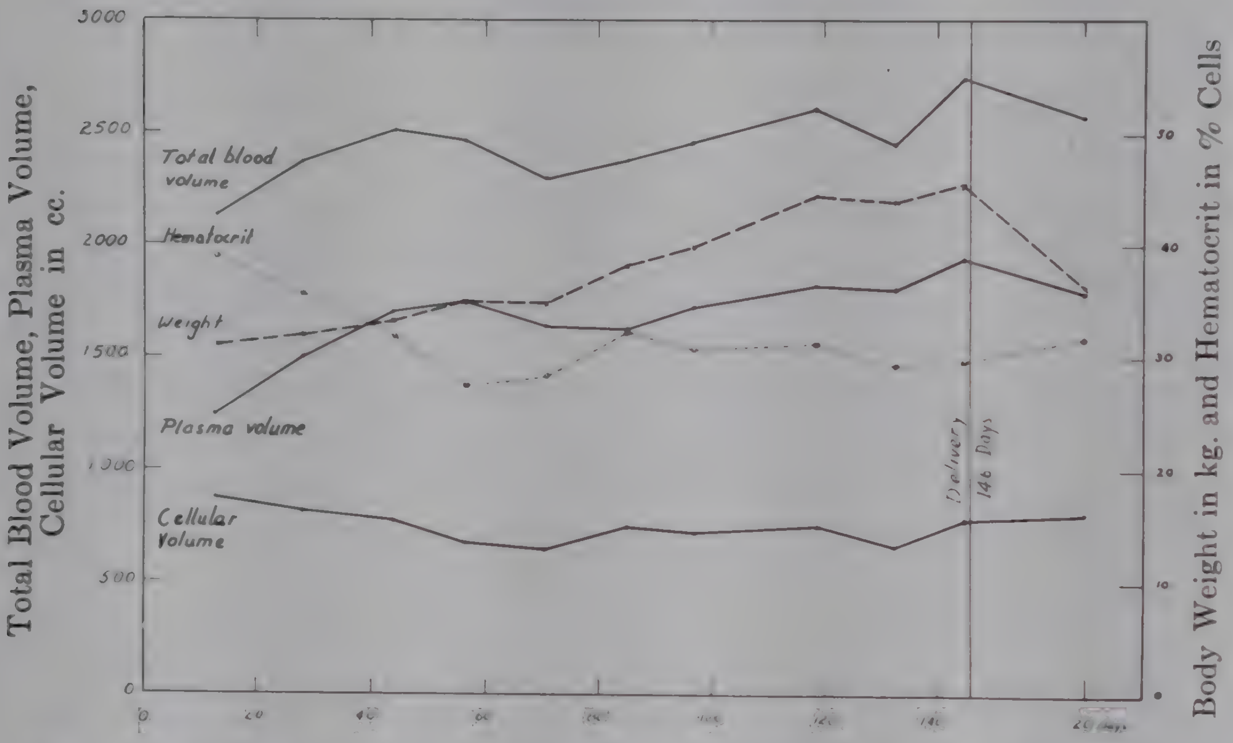

FIG. 15.—Total blood volume, hematocrit readings, plasma volume, cellular volume, and body weight of a pregnant sheep. Note the rise in blood volume and plasma volume as pregnancy advances. The cellular volume falls slightly; hence the increase in blood volume is accounted for by an increase in plasma volume. (Redrawn and slightly modified from Barcroft, Kennedy, and Mason, *Journal of Physiology*, 1939, 95.)

Blood Substitutes. Extensive search has been made for substances that can be used to restore the blood volume after hemorrhage, during shock, and in other conditions. Following are some of the substances that have been tried: (1) Isotonic sodium chloride solution (0.9 per cent). While physiological saline solution is inferior to some other blood substitutes, recent work shows that the infusion of large amounts of saline (15 to 20 per cent of body weight), as after massive hemorrhage, has definite value. The diluting effect of saline on the blood proteins, thereby tending to cause the passage of an excessive amount of water from the blood into the tissues, is not now regarded as being as serious an objection to the use of saline intravenously as was formerly thought. Ivy and co-workers showed that injections of 0.9 per cent of sodium chloride into dogs after severe blood loss caused a significant reduction in mortality as compared with the untreated group. (2) Hypertonic saline and glucose solutions. These are used, although there is no certainty that the strong glucose solutions sometimes employed (35 per cent or more) in cases of reduced blood volume have any great advantage over isotonic glucose solutions (Wiggers). However, glucose has the advantage that it can be oxidized for energy purposes when given in this way. (3) Colloidal solutions. Because of the larger size of their molecules, colloids pass through the capillary endothelium less readily than crystalloids and therefore hold water in the blood vessels by reason of their osmotic pressure (p. 70). A number of colloidal solutions have been used as blood substitutes. Acacia in saline, pectin in saline, and gelatin in saline are examples. None of these substances can be regarded as complete substitutes for plasma. Details regarding their advantages and disadvantages may be found elsewhere (Moon; Wiggers; Landis, 1945). (4) Serum, plasma, and whole blood.

Chapter III

LYMPH; CEREBROSPINAL FLUID; SYNOVIAL FLUID

IN most places in the body the blood vascular system is closed, the blood itself not coming into direct contact with the tissue cells. Their nutrition is maintained through the intermediation of a fluid formed from the blood and termed tissue fluid. This fluid has been described as a "middleman" between the blood and tissues. It enables oxygen and nutrient materials to pass from the blood to the tissues, and carbon dioxide and other waste products to pass from the tissues to the blood. Fluid in the tissue spaces may be returned to the blood capillaries directly, or it may be drained away as lymph by a system of lymph channels. These begin in the tissues as blind lymph capillaries, similar in structure to blood capillaries. By the convergence of lymph capillaries, smaller lymph vessels are formed, and these in turn unite to form larger lymph vessels. The structure of lymph vessels is similar to that of veins, although the former have thinner walls. Ultimately all lymph vessels drain into either the thoracic duct or the right lymphatic duct, which empty into the venous system anterior to the heart. Lymph from the right side of the head and neck, the right foreleg, and the right side of the thorax is returned to the venous system by the right lymphatic duct; that from the rest of the body, by the thoracic duct. Upon entering the blood the lymph becomes a part of the blood, its identity as lymph being lost.

As is discussed elsewhere (Chapter VII), many of the blood vessels of the body are under motor control. The thoracic duct is also under motor control. Acetylcholine causes a constrictor effect on the duct, adrenaline a dilator effect. Stimulation of the vagus nerve causes, like acetylcholine, a constrictor effect (Acevedo).

The Function of Lymph Nodes. Lymph on its way to the blood stream via the system of lymph vessels apparently must pass through at least one lymph node. In many instances more than one node is encountered. It is generally agreed that lymph nodes have at least two functions. One of these is the production of lymphocytes, of which the lymph nodes contain large numbers. These cells are added to the lymph current as it slowly passes through the node. Lymph contains very few cells until a lymph node is traversed.

Another function of lymph nodes is to stop foreign material that comes to them in the lymph. This filtration is believed to be accomplished mechanically and by the phagocytic activity of the reticulo-endothelial cells. Experiments of Drinker, Field, and Ward indicate that normal lymph nodes are very efficient filters. This was determined in anesthetized dogs by perfusion of nodes with solutions containing erythrocytes and streptococci. The "efficiency was so great as to make it fairly certain that in a part kept at rest early in an infection practically no microorganisms would escape the nodes in the line of drainage."

In gallinaceous birds and pigeons lymph nodes are absent. In swimming birds they are present but not numerous. The bone marrow of birds contains numerous nodules of lymphoid tissue, apparently to compensate for the absence of lymph nodes in these species (Jordan). These medullary lymph nodules increase in number following splenectomy (Jordan and Robeson).

COMPOSITION OF LYMPH

Although in these discussions tissue fluid and lymph proper, that is, the fluid in the lymph vessels, are assumed to be of the same composition (Drinker and Yoffey), there is no proof that such is the case. The difficulty involved is not that of obtaining samples of lymph. These can be collected by inserting a cannula into the thoracic duct or other lymph vessel. The problem is one of obtaining a sample of pure tissue fluid under perfectly normal conditions. Many attempts have been made, but it is difficult to be certain that the sample obtained is not contaminated with other fluids. The recent work of Maurer on the isolation and analysis of extracellular muscle fluid may be cited.

Lymph, derived largely from the blood, is similar in composition to blood plasma. The plasma of the blood passes through the thin wall of the blood capillaries, enters the tissue spaces, and becomes tissue fluid or lymph. The cells of the tissues themselves also contribute somewhat to the composition of lymph, for there is a free interchange between the fluid in the cells (tissue juice) and the fluid in the tissue spaces. In this way the cells rid themselves of waste products of metabolism and absorb foodstuffs.

The composition of lymph varies with the state of activity of the digestive organs; lymph derived from the intestine during fat absorption has a milky appearance and is known as chyle. Ordinarily lymph is a clear, colorless, watery liquid having a specific gravity of about 1.015. It contains a few red corpuscles normally, and lymphocytes are present. The latter cells are more abundant in lymph that has passed through lymphoid tissue. Whether or not monocytes are present is uncertain. Neutrophilic leucocytes are ordinarily absent; however, they may be present in great numbers in infections. Platelets are said to be absent; nevertheless lymph will clot, though feebly. The liquid part after clotting has occurred is designated as lymph serum. Lymph contains water, gases, proteins, nonprotein nitrogenous substances, glucose, inorganic salts, hormones, enzymes, vitamins, and immune substances. The proteins are the same in kind as in blood plasma but the amount is less. This is especially true of lymph from the limbs, for the capillary walls in these regions are less permeable to the blood proteins than in other regions. The protein content of lymph from different species and different lymphatics is shown in the accompanying table. Values are also given for the protein content of blood serum.

PROTEIN CONTENT OF BLOOD SERUM AND LYMPH

Species	Source of Lymph	Protein (gm. per 100 cc.)	
		Serum	Lymph
Lamb	Cervical lymphatics	5.81	3.64
Dog	Thoracic duct	6.25	4.00
Dog	Cervical lymphatics	6.25	3.63
Dog	Leg lymphatics	6.46	1.91
Dog	Intestinal lymphatics	6.23	3.98
Dog	Liver lymphatics	6.34	5.32
Rabbit	Thoracic duct	—	3.53
Monkey	Cervical lymphatics	5.12	3.48
Man	Deep pelvic lymphatics	7.8	5.5

(Data from Drinker and Yoffey.)

A study has been reported of the rate of flow and the normal composition of the lymph from the forelegs of calves. The percentage of protein in the blood serum varied from 5.4 to 6.7, in the lymph from 2.2 to 3.1 (Glenn, Muus, and Drinker).

Since lymph is a filtrate from the blood, one would expect to find the crystalloid content of lymph and of blood plasma to be very similar. Analyses reveal that this is true. There are some small quantitative differences, however, in the electrolyte pattern which are determined by the lower protein content of lymph. Thus lymph shows higher chloride and bicarbonate concentrations than does serum (Drinker and Yoffey). It is probable that these differences are explainable in terms of the

Donnan equilibrium. The freezing point of lymph is substantially the same as that of blood serum. The *p*H of lymph (cervical) is slightly higher than that of plasma.

FORMATION OF LYMPH

Two principal views have been held regarding the mechanism of lymph formation. One is a physical view and the other may be designated as a secretory or physicosecretory view. Modern opinion and evidence are decidedly in favor of the physical view. According to this the known facts regarding the formation of lymph can be explained on the basis of hydrostatic, osmotic, filtration, and diffusion pressures, and probably other physical or physicochemical processes. Few modern physiologists find it necessary to assume a secretory activity of the capillary or tissue cells in lymph production. Most workers feel that further progress will come along the physical or physicochemical pathways. The basis of our present concepts regarding the formation of lymph may be found in the researches and writings of Starling, Bayliss, Krogh, McLean, Landis, Drinker and co-workers, and others.

The hydrostatic pressure in the capillaries is the capillary blood pressure, and it is an important force in the exchange of fluid between the blood and the tissue spaces. At the arterial end of the capillary, the capillary pressure is equal to some 35 mm. Hg, whereas at the venous end it has fallen to perhaps 15 mm. Hg. This force tends to drive water and dissolved substances through the capillary wall, but it is counteracted to a large degree by the osmotic pressure of the plasma proteins. These, because of their large molecular size, cannot readily pass through the capillary wall. Crystalloids, such as inorganic salts, urea, glucose, and other small molecules, easily pass through the membrane and therefore do not exert an effective osmotic pressure within the capillary. The pioneer work of Starling and the subsequent researches of other investigators have shown that the blood proteins possess a low but relatively constant osmotic pressure of about 22 mm. Hg. It has been calculated that nearly 80 per cent of the colloid osmotic pressure of the blood is due to the albumins, which are of smaller molecular size than the globulins (Cohn). The osmotic pressure of the plasma proteins increases slightly as the blood traverses the capillary because water passes out and the concentration of the protein therefore rises.

In arriving at a conception of the forces concerned in lymph production, one must take into account not only the hydrostatic and osmotic pressures within the capillaries but also the same forces in the tissue spaces. In the tissues there is a small hydrostatic pressure known as the tissue pressure. Attempts to determine the magnitude of this pressure have not been very successful. In subcutaneous tissues it apparently ranges from 0 to 6 mm. Hg. Intramuscular pressure during muscular contraction may be much higher (Wells, Youmans, and Miller). Intramuscular pressure in anesthetized dogs has been recorded at 4 to 5 mm. Hg.

Permeability of the capillary wall to the plasma proteins is not the same in all situations in the body and under all conditions. Liver capillaries appear to be especially permeable, whereas limb capillaries are much less so. As a result of this differential permeability, a variable amount of protein passes through the capillary wall into the tissue spaces. The magnitude of the osmotic pressure exerted by this protein obviously varies with the protein content of the tissue fluid, but a value of 8 mm. Hg may be taken for illustration. As to changes in the permeability of the wall of individual capillaries, not a great deal of positive information is available. Products of metabolism entering the capillaries are thought to enhance their permeability, and dilatation of the capillaries, however brought about (p. 189), would doubtless increase their permeability.

The relation of these various pressures at the arterial and venous ends of the capillary may be summarized as follows:

Interchange Between Blood and Tissue Fluid

	Blood	Tissue fluid
Arterial end of capillary	Capillary pressure = 35 mm. Hg	Tissue pressure = 5 mm. Hg
	Effective hydrostatic pressure (35 − 5) = 30 mm. Hg ——	——→
	Osmotic pressure = 22 mm. Hg	Osmotic pressure = 8 mm. Hg
	Effective osmotic pressure (22 − 8) = 14 mm. Hg ←——	——
	Filtration force (30 − 14) = 16 mm. Hg	
Venous end of capillary	Capillary pressure = 15 mm. Hg	Tissue pressure = 5 mm. Hg
	Effective hydrostatic pressure (15 − 5) = 10 mm. Hg ——	——→
	Osmotic pressure = 25 mm. Hg	Osmotic pressure = 8 mm. Hg
	Effective osmotic pressure (25 − 8) = 17 mm. Hg ←——	——
	Absorbing force (17 − 10) = 7 mm. Hg	

Filtration therefore occurs at the arterial end of the capillary and absorption at the venous end.

Hemorrhage causes a lowering of the capillary pressure but not the osmotic pressure of the blood colloids. This is believed to be an important factor in determining increased absorption from the tissues into the blood after blood loss. Physiological salt solution injected into the blood stream, as after hemorrhage, increases the capillary blood pressure while lowering the osmotic pressure of the blood proteins. Increased filtration results. This is the reason why physiological salt solution is not as well retained in the vascular system as are solutions containing colloidal material.

A recent study of the effect of variations in the perfusion (hydrostatic) pressure and in the osmotic pressure of the perfusion fluid on the rate of filtration across the capillary wall has been made by Hyman.

Another factor in lymph production is increased tissue activity. This involves the breaking down of large molecules into numerous smaller ones. These diffuse into the tissue spaces and increase the diffusion pressure of the tissue fluid. This causes diffusion currents to be set up from the blood to the tissues, with the result that the amount of the tissue fluid is increased.

Studies in which heavy water was injected into the blood indicate a very rapid passage of water through the capillary wall (Hertzman).

FUNCTIONS OF LYMPH

The part played by lymph in the normal workings of the body has been suggested above. It may be stated again that the chief function of lymph is to act as a medium of communication between the blood and tissues, allowing nutrient material to pass from the blood to the tissues and waste products to pass in the opposite direction. It also transports absorbed fat from the intestine to the blood, and, by virtue of its lymphocytes, it is concerned in the defense of the body against invading microorganisms.

FLOW OF LYMPH

Lymph in the tissue spaces is in communication with the blood in the capillaries, the juice in the cells, and the lymph in the lymph capillaries. The latter remove from the tissue spaces materials that do not or cannot enter the blood capillaries. Water and crystalloids can move either way. Particulate matter and large molecules such as proteins and lipids cannot enter the blood capillaries, but can penetrate the much more permeable walls of the lymph capillaries (Peters, Drinker).

The flow of lymph in the lymph vessels is sluggish and in one direction only—from the tissues toward the heart. The factors concerned in lymph flow are: (1) the difference in pressure at the two ends of the lymph system; (2) the massaging effect of muscular movements; and (3) the presence in the lymph vessels of valves, which permit flow in one direction only.

With reference to the first factor, the pressure in the lymph capillaries is higher than the pressure at the point of entrance of the thoracic duct into the venous system. The latter pressure is still further lowered at every inspiration by the aspiratory action of the thorax. Lymph therefore flows toward the venous system. The flow of lymph toward the thorax is further augmented, during inspiration, by the backward movement of the diaphragm, which increases the pressure in the abdomen and thus assists in emptying its lymphatics toward the thorax. The second and third factors are of importance in lymph flow. The lymph vessels have very thin walls. It follows, therefore, that any outside pressure, such as that produced by the contraction of skeletal or visceral muscle, will tend to compress their walls and thus to force lymph toward the heart, back flow being prevented by valves in the vessels.

Edema. Whenever the production of lymph is in excess of its removal from the tissues, an accumulation of lymph results, and the condition is known as edema or dropsy. Landis (1937) lists the following primary and contributory factors in the production of edema: primary—(1) increased capillary pressure, (2) lowered osmotic pressure of the blood colloids, (3) injury to the capillary wall, (4) impaired drainage of lymph; contributory—(1) low tissue pressure, (2) high salt intake, (3) high intake of fluid, (4) warm environmental temperature, (5) disturbances of innervation.

CEREBROSPINAL FLUID

The Meninges and the Cerebrospinal Pathway. The meninges are the membranes surrounding the brain and spinal cord. The outermost of these coverings is the thick, fibrous dura mater. Beneath this is the delicate subdural space, containing a film of fluid. Forming the inner wall of this space is the arachnoid, which sends, from its inner surface, numerous delicate trabeculae into the extensive subarachnoid space. These trabeculae extend down to the pia mater, a highly vascular membrane closely investing the spinal cord and brain and adhering to them. The two innermost membranes, the arachnoid and the pia mater, are sometimes collectively designated as the leptomeninges or the pia-arachnoid.

The subarachnoid space, its perivascular extensions, the ventricles of the brain, and the central canal of the spinal cord collectively constitute the cerebrospinal pathway, which contains the cerebrospinal fluid. The subdural space has no anatomical and probably no physiological connection with the subarachnoid space.

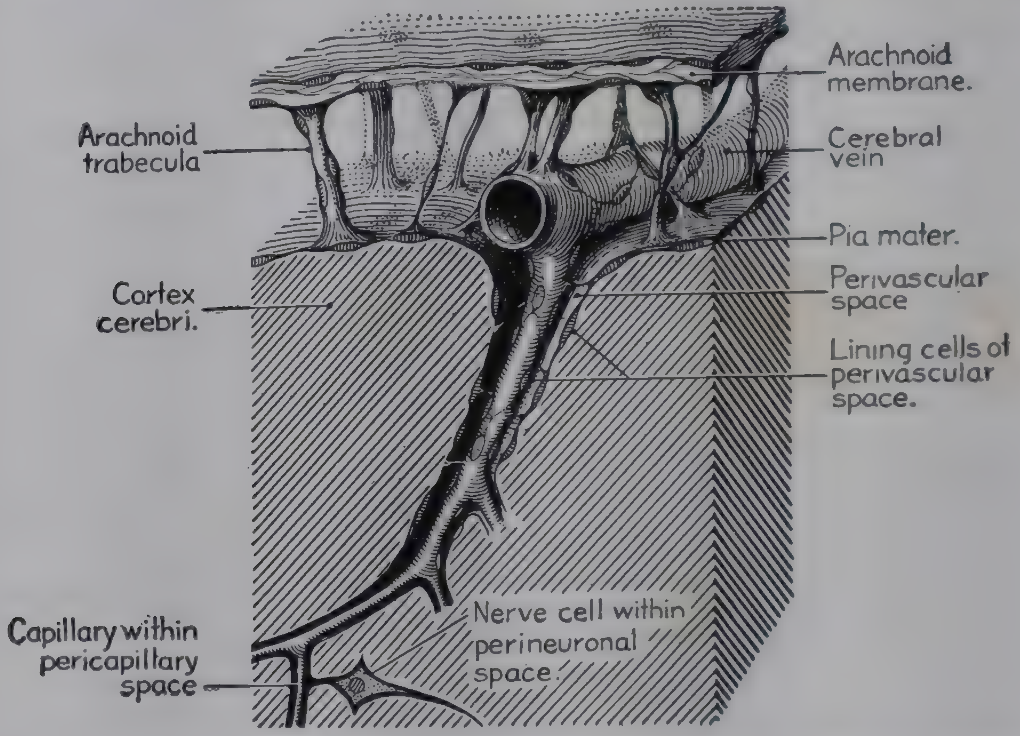
Arachnoid membrane.
Arachnoid trabecula
Cerebral vein
Pia mater.
Cortex cerebri.
Perivascular space
Lining cells of perivascular space.
Nerve cell within perineuronal space.
Capillary within pericapillary space

Fig. 16.—Schematic representation of the arachnoid membrane, pia mater, and nervous tissue to show the relations of the subarachnoid, perivascular, and perineuronal spaces. (Weed; from Wislocki's "The Cytology of the Cerebrospinal Pathway," in Cowdry's *Special Cytology,* Paul B. Hoeber, Inc.)

Properties of the Cerebrospinal Fluid. Derived from the blood, cerebrospinal fluid is thin and watery, and normally contains no constituents not present in blood. Fibrinogen and some other substances with large molecules (lipids, most enzymes, etc.) are absent from cerebrospinal fluid, but its contains a very small amount of protein. Most crystalloids present in blood are also present in cerebrospinal fluid but in many instances in reduced amounts. Sodium, potassium, urea, and possibly glucose are present in approximately equal amounts in the two fluids, and the latter have the same *p*H. Chlorides predominate in cerebrospinal fluid. This fluid normally contains no cellular elements except a few lymphocytes. In certain pathological conditions leucocytes may be present.

Studies of the cerebrospinal fluid of normal cattle (Carmichael and

Jones) indicate the following average composition (mg. per 100 cc. of the fluid): total protein, 34; glucose, 37; chlorides (as NaCl), 685; urea nitrogen, 11; nonprotein nitrogen, 16; creatinine, 1.4; calcium, 5.5. The *p*H of the cerebrospinal fluid of cattle is 7.4 to 7.6, the specific gravity 1.006 to 1.007 (Fedotov). Studies of the composition of the cerebrospinal fluid of horses have been made (Fedotov).

Origin and Circulation. The cerebrospinal fluid comes from the blood. A large amount of morphological and experimental evidence indicates that the principal site of its elaboration is the choroid plexuses of the ventricles of the brain (Weed, 1922; Fremont-Smith). In addition to the quota of liquid derived from this source, a small amount is derived from the perivascular and perineuronal spaces of the brain. These are delicate spaces surrounding the blood vessels and nerve cells and communicating with the subarachnoid space (Fig. 16). The production of cerebrospinal fluid is continuous.

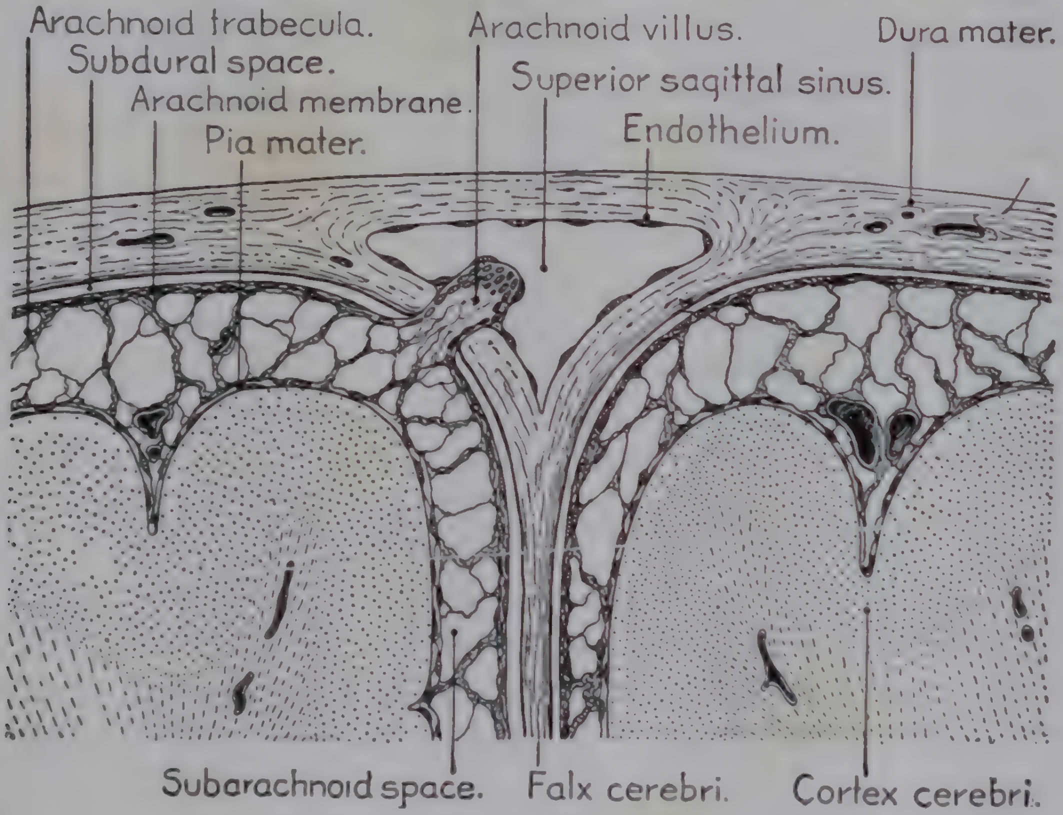
Arachnoid trabecula.
Subdural space.
Arachnoid membrane.
Pia mater.
Arachnoid villus.
Superior sagittal sinus.
Endothelium.
Dura mater.
Subarachnoid space.
Falx cerebri.
Cortex cerebri.

FIG. 17.—Schematic representation of the meninges and cerebral cortex to show the relation of an arachnoid villus to a dural venous sinus. (Weed; from Wislocki's "The Cytology of the Cerebrospinal Pathway," in Cowdry's *Special Cytology*, Paul B. Hoeber, Inc.)

The choroid plexuses consist of very vascular cores covered with a single layer of epithelial cells. How these plexuses give origin to the cerebrospinal fluid is not entirely known. Some workers maintain that the process is one of active secretion; others believe that it is essentially one of filtration, in which the filtering force is equal to the blood pressure in the capillaries of the choroid plexus less the osmotic pressure of the blood colloids and the cerebrospinal fluid pressure (Menninger, Fremont-Smith). On the basis of the latter view, the mechanism would be similar to that employed in lymph production and in the initial formation of urine. From thermodynamic considerations of the present evidence Flexner concludes that cerebrospinal fluid is a secretion and not a dialyzate or an ultrafiltrate. He says that "the pressure in the capillaries of the choroid plexus is too small to account for the free energy change which takes place in the formation of the fluid."

The cerebrospinal fluid from the lateral and third ventricles enters the fourth ventricle, from which it passes out through the roof into the subarachnoid space. Three foramina are usually described in the roof of the fourth ventricle, but all three may be artifacts. If the latter is true, the fluid would have to pass through an intact membrane. After entering the subarachnoid space, the ventricular fluid passes downward in the spinal subarachnoid space and upward over the brain, mixing, as it flows, with the fluid derived from the perivascular and perineuronal spaces. Its movement is facilitated by the pulsations transmitted from the blood vessels. In the central canal of the spinal cord, the ventricles of the brain, and the subarachnoid space, therefore, the cerebrospinal fluid slowly circulates.

Pressure. The cerebrospinal fluid pressure has been measured in different species. A common method is to insert a needle into the cisterna magna and to connect the needle to a manometer containing Ringer's solution or physiological saline. In anesthetized dogs pressures of 110 to 120 mm. Ringer's solution are commonly seen. In young cattle pressures ranging from 80 to 150 mm. saline, with an average of 105 mm., have been observed. In vitamin-A deficiency in young bovines the cerebrospinal fluid pressure is elevated; at the terminal stage pressures 4 to 6 times the normal may be seen (Moore and Sykes, 1940, 1941; Sykes and Moore).

Considerably higher pressures have been found in horses than in normal dogs or normal cattle (Fedotov).

Absorption. The constant formation of cerebrospinal fluid implies its constant absorption. As it circulates in the subarachnoid spaces, it is brought into contact with the tiny arachnoid villi, through which it is removed into the adjacent venous sinuses. These villi are projections from the arachnoid through the dura mater into the dural venous sinuses (Fig. 17). It is through these villi that the cerebrospinal fluid is forced into the venous blood of the sinuses. That the major part of the liquid is removed in this way is evident from the anatomical and experimental studies of Weed. In addition a much less important, slow drainage has been demonstrated to occur, by way of the perineural spaces of the spinal and cranial nerves, to the lymphatic vessels.

The force concerned in the absorption of cerebrospinal fluid appears to be derived from the subarachnoid pressure and the osmotic pressure of the blood colloids less the opposing intracranial venous pressure (Weed, 1935).

Amount. The amount of the cerebrospinal fluid in man is some 60 to 80 cc. By cisternal puncture in horses, 170 to 300 cc. of fluid can be obtained at a time (Fedotov).

Functions. Filling the central canal of the spinal cord, the ventricles of the brain, and the subarachnoid space, the cerebrospinal fluid serves as a cushion for the brain and the spinal cord. This is its best-known and perhaps most important function. Another function of the liquid is related to the presence of the perivascular and perineuronal spaces. In lieu of a true lymphatic system, the central nervous system seems to use these channels for the elimination of fluid into the subarachnoid space. Lastly, changes in the amount of blood in the cranium are compensated for by changes in the amount of cerebrospinal fluid. Thus the volume of the cranial contents remains constant.

SYNOVIAL FLUID AND THE JOINT CAVITY

Synovial fluid is the liquid contained in a joint cavity. The physical and chemical properties of the normal fluid and its method of formation have not been extensively investigated. Recently Ropes, Bennett, and Bauer made a study of the synovial fluid obtained by aspiration from the tibiotarsal joint of young cattle. Samples of arterial blood for comparative study were also procured. The amount of fluid obtained from a single joint varied from 20 to 50 cc. The fluid was clear, straw-colored, and viscid. The average number of nucleated cells was 131 per cubic millimeter. The relative viscosity was 3.72 on the average. The average *p*H (7.31) was slightly lower than that of blood serum. The total protein content was about one per cent. The protein consisted mainly of albumin, but globulin and mucin were present. Fibrinogen was absent. Other studies show that the concentration of mucin varies greatly in the fluid from different joints.

The composition of the fluid when compared to that of blood serum was such as to support the theory that synovial fluid is a dialyzate of the blood plasma. Anatomical studies of the subsynovial vascular supply accorded with this view.

The origin of mucin was not determined. The suggestion was made that it is formed by the connective tissue cells surrounding the joint.

There was evidence that mucin, in addition to its lubricating action, helps to regulate the exchange of water and other substances between the blood and the joint cavity.

Functions. The best-known function of synovial fluid is to lubricate the articular surfaces. Another function is to nourish the articular cartilages. They lack a blood supply and therefore are dependent on synovial fluid for their metabolic exchanges.

The physiology of articular structures is the subject of a review by Bauer, Ropes, and Waine.

Absorption from the Joint Cavity. This has been studied by Adkins and Davies, using the knee-joint of the rabbit. True solutions, colloidal solutions, and fine suspensions are removed from the joint cavity into the subsynovial tissues rather quickly. The rate of removal is directly related to the size of the particles. The experiments suggested that physical forces were mainly concerned in the removal.

Particle size determines the route of removal of substances that have entered the subsynovial tissues. Small particles, as in true solutions, easily enter both the blood capillaries and the lymph capillaries, but most are removed by the former. Small colloidal particles enter both kinds of capillary, but with less ease. Particles about the size of the globulin molecule are not taken into the blood capillaries at all, and only to a slight extent into the lymphatics. Particles of still larger size—for example, 100 millimicrons—have no route of removal from the subsynovial tissues.

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PART II

The Circulation of the Blood

Chapter IV

THE PHYSIOLOGY OF THE HEART

THE heart is a hollow muscle situated in the middle mediastinal space. The mammalian heart has four chambers; the upper two are designated the atria, the lower two the ventricles. There is a complete septum between the two sides of the heart; however, there is free communication between the atrium and ventricle on the same side. The right side of the heart is the venous or pulmonary side, the left the arterial or systemic side. The ventricular wall is much thicker than the arterial wall, and the left ventricular wall is much thicker than the right.

The heart presents four valves, two on each side, whose purpose is to prevent backflow of blood. The valves between atria and ventricles, one on each side, guard the atrioventricular orifices and are designated the atrioventricular or A-V valves. The one on the left side is known also as the bicuspid or mitral valve; the one on the right side also as the tricuspid valve. A valve stands at the aortic orifice and one at the pulmonary orifice. These are known respectively as the aortic and the pulmonary valve.

THE COURSE OF THE CIRCULATION

If a given particle of blood could be followed from the moment it left a certain point in the circulation, say the left ventricle, until it returned to the same point, its general route would be found to be as follows. Leaving the left ventricle, it would enter the aorta, from which it would pass by a series of arteries, varying with the exact route taken, to the systemic capillary area. Traversing the capillaries, it would enter the venous system, by which it would return to the right atrium. From this point it would pass into the right ventricle and thence by way of the pulmonary artery (as venous blood) to the pulmonary capillaries. Leaving these, it would return by way of the pulmonary veins (as arterial blood) to the left atrium, whence it would go to the left ventricle, thus completing the circuit. A diagram of the mammalian blood circulation is shown in Fig. 18.

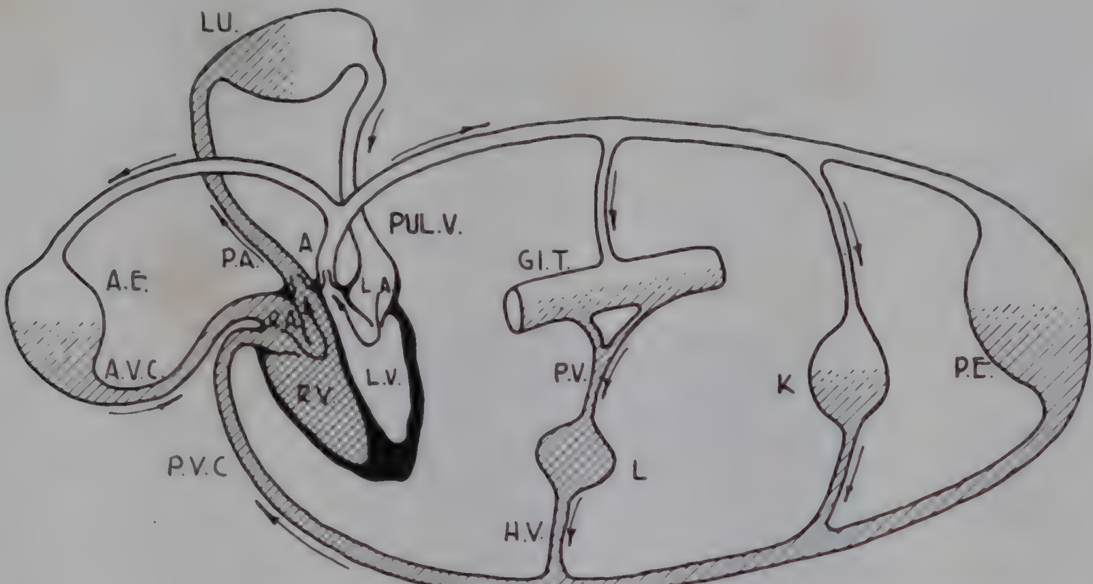

FIG. 18.—Schematic representation of the mammalian blood circulation. R.A., right atrium; R.V., right ventricle; L.A., left atrium; L.V., left ventricle; GI.T., gastro-intestinal tract; K, kidney; P.E., posterior extremities; P.V., portal vein; L, liver; H.V., hepatic veins; P.V.C., posterior vena cava; A.E., anterior extremities; A.V.C., anterior vena cava; P.A., pulmonary artery; A, aorta; Lu., lungs; Pul.V., pulmonary veins. The venous side of the circulation is shaded.

RHYTHMICITY OF AND CONDUCTION IN THE HEART

The Pacemaker. In the beat of the heart the normal sequence is a nearly simultaneous contraction of the atria followed by a nearly simultaneous contraction of the ventricles. The right atrium contracts a fraction of a second before the left (Wiggers), and the synchronism of the contraction of the two ventricles is not so perfect as was formerly thought (Katz, 1925).

The beat begins in the sino-atrial or S-A node, which is situated in the wall of the right atrium. In the mammalian heart this node corresponds physiologically to a well-developed chamber in the heart of lower vertebrates (frogs, etc.) called the sinus venosus, into which the great veins open; the sinus communicates freely with the right atrium. That the sinus venous is the place of origin of the heart beat in such animals is indicated by the observations of a number of authorities. Stannius' experiment is classical: a ligature is tied around the sino-atrial junction, whereupon the atria and ventricle stop beating, while the sinus continues to beat. In the hearts of mammals, the principal remnant of the sinus venosus is found in the wall of the right atrium between the openings of the anterior vena cava and the coronary sinus. In this region there is a special area of modified cardiac muscle fibers, with some nervous tissue, called the sino-atrial node.

It extends from about the root of the anterior vena cava to a point midway between this vessel and the coronary sinus. The sino-atrial node has been designated the pacemaker of the heart, and that the normal heart rhythm is dominated by the node is indicated by a number of facts such as the following. (1) Excision or destruction of the node causes the heart beat to cease or to become slower. (2) Slight changes of temperature in the region of the node cause alterations of the heart rate, whereas similar changes of temperature in surrounding places are ineffective. (3) By means of a delicate galvanometer or potentiometer, electrical negativity—a never-failing manifestation of protoplasmic activity—can be demonstrated to occur, during the heart beat, first at the sino-atrial node. However, evidence has been adduced that tissue in the immediate vicinity of the node may also give origin to impulses for cardiac action.

An anatomical study of the region of the S-A node of domestic animals has been made by Glomset and Glomset.

Conduction. The impulses generated in the pacemaker spread to the atria, probably in a radial manner through the general atrial musculature. A structure analogous to the atrioventricular bundle, by which the impulses pass from atria to ventricles, is not found in the atria. The velocity of the impulse in the atria is comparatively low, varying between 0.8 and 1.2 meters per second.

In the hearts of lower vertebrates there is direct muscular continuity between the atria and ventricles. In the hearts of mammals, on the other hand, fibrous connective tissue is developed at the atrioventricular junction, into which tissue the musculature of the atria and ventricles is largely inserted. Years ago it was thought that this ring of connective tissue completely separated the musculature of the atria from that of the ventricles. It is now known that there is muscular connection between the upper and lower chambers. This connection is effected mainly by the atrioventricular or A-V bundle (Fig. 19), which is composed chiefly of modified cardiac muscle cells. The bundle begins in the region of the coronary sinus. The fibers from this region converge toward a thickened area termed the artioventricular node, which is situated at the base of the interatrial septum on the right side and near its posterior margin. From this node the bundle passes along the top of the septum between the ventricles and divides into two branches, one for the right ventricle and one for the left. These branches run under the endocardium, dividing and redividing in a complex manner and forming an extensive arborization on the inner surface of the ventricular wall (Purkinje fibers). Some strands cross the cavity of the right ventricle as a part of the "moderator" band, which in the sheep has been found to be made up of 10 to 16 per cent of Purkinje fibers (Atkinson). The arborization beneath the endocardium is especially well seen in the fresh heart of ungulates (Holmes). The subendocardial network is continued into the wall of the heart by an extensive myocardial Purkinje network.

The atrioventricular conduction system of the ox heart, including its myocardial ramifications, has been studied by Cardwell and Abramson, who present a number of excellent anatomical illustrations of their injections and dissections of the heart. The morphology of the ventricular conduction system in domestic animals has been studied by Glomset and Glomset. The incidence and size of the moderator band in animals has been investigated by Truex and Warshaw.

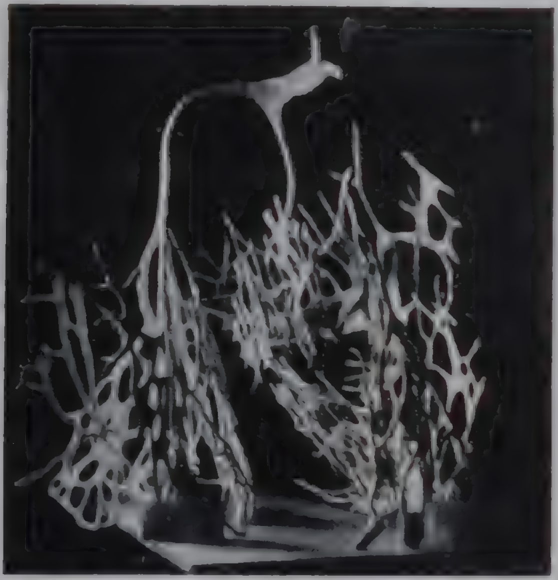

FIG. 19.—Photograph of a model of the atrioventricular bundle of a calf's heart. The complete network in the outer wall of the left ventricle is not shown. (From De Witt, *Anatomical Record,* published by the Wistar Institute.)

The function of the A-V node and bundle is to receive the excitatory impulse from the atria and pass it to the ventricles. Although nerve fibers and nerve cells form an important part of the bundle, the evidence indicates that the impulse is conducted by the muscle component of the bundle. The conduction velocity in the bundle, 3 to 5 meters per second, is several times higher than in the atria. It is so rapid and the distribution of the bundle to the ventricles so complete that all portions of the ventricular mass are thrown into contraction nearly simultaneously.

Conduction of the impulse through the A-V node is slower than through the rest of the conducting system. The resulting brief delay allows atrial contraction to be completed before the ventricles are stimulated (Wiggers).

Normally the rhythm of the entire heart is dominated by the S-A node. Under some conditions excitatory impulses may originate outside this node. They are known as *ectopic impulses* and the resulting series of beats is known as an *ectopic rhythm*. If the S-A node is injured or destroyed, the A-V node may become the origin of ectopic impulses, that is, may assume the role of pacemaker. If the A-V bundle is cut, compressed, or greatly diseased, the ventricles are cut off from the pacemaking influence of the atria and develop an independent rhythm dominated by an ectopic center in the A-V bundle somewhere below the point of injury. The ventricular rate under these conditions is usually slow.

The conducting system in the avian heart has not been as fully studied as has that in the mammalian heart. The evidence indicates that the system is not as extensive in birds as in mammals (Clark, 1927). In the heart of the ostrich a system of fibers somewhat similar to the A-V bundle of mammals has been described (Drennan).

Readers who wish further information on the origin and conduction of the heart beat will find the following references valuable: Eyster and Meek, 1921, Flack, Wiggers, Lewis.

ELECTRICAL CHANGES ACCOMPANYING THE HEART BEAT

If two points on the surface of an uninjured muscle or nerve are connected by means of electrodes to a sensitive galvanometer or other electrical detector, no deflection of the instrument occurs. This is because all parts of the tissue are at the same electrical potential, that is, in the isoelectric state. If one end of the tissue is stimulated, the active end become electrically negative to the resting, and as a result a wave of

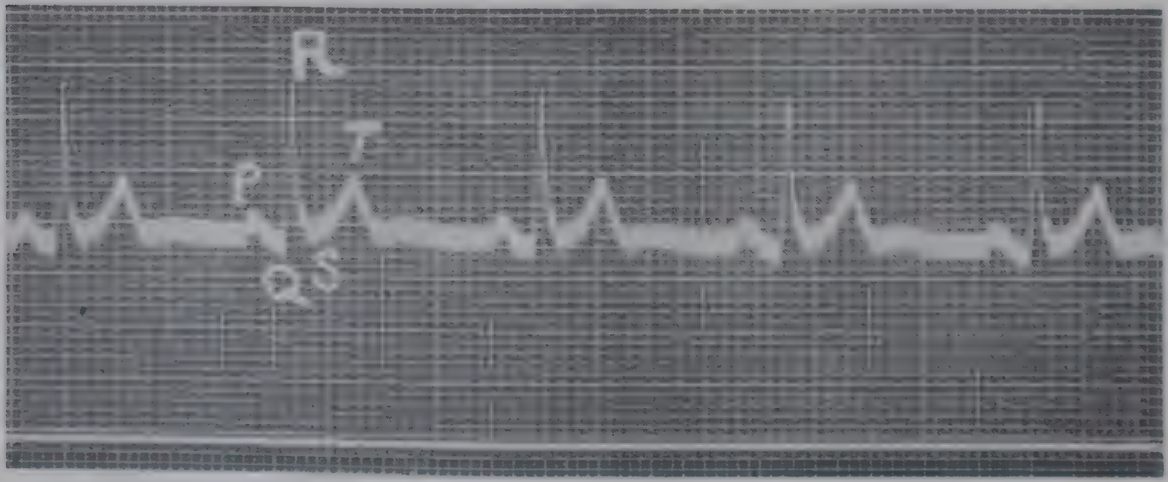

FIG. 20.—Electrocardiogram of a man. The S wave is practically absent. The vertical lines show time; they are 0.04 sec. apart. The horizontal lines show voltage; each division is 0.1 millivolt.

negativity, or an electrical disturbance, passes to the positive or resting end. The presence of this electrical change that passes along the tissue may be shown by a galvanometer, potentiometer, or other detecting device connected to the tissue by means of electrodes. The deflections of the instrument caused by the changes of potential under the electrodes may be recorded photographically. Such a record shows two deflections and is therefore said to be diphasic. The first deflection occurs when the electrical change passes under the first electrode, the instrument showing that this part of the tissue is negative to the part under the other electrode. The second deflection, opposite in sign, occurs when the wave passes under the second electrode, this part of the tissue now being negative.

As with active protoplasm in general, so with the heart during contraction, electrical changes, or action potentials, are produced. They may be detected by a simple biological method. The thorax of an anesthetized animal is opened and artificial respiration is provided; the heart continues to beat. A sciatic-nerve–gastrocnemius muscle preparation of a frog is made. By holding the isolated leg of the frog in such a position that the nerve touches the ventricle at two points, one observes that the gastrocnemius muscle contracts and the leg twitches at every systole of the heart. The action potentials of the heart have stimulated the nerve, thus causing the muscle to contract and the leg to twitch.

Another way of detecting the action potentials of the heart, as well as recording them, is to use the very sensitive string galvanometer. This consists essentially of a delicate conducting fiber or "string" suspended in a narrow gap between the poles of a powerful electromagnet. The string is made of glass or quartz covered with silver, gold, or other conducting material. If a minute electric current is passed through the string lying in the powerful magnetic field, or if a potential difference is impressed upon the string, it bends, or deflects slightly, in a plane parallel to the faces of the pole pieces of the electromagnet. The direction of movement of the string depends on the direction of the current passing through it. If the current passes downward, the deflection of the string is toward the observer. If the current passes upward, the string moves away from the observer. The deflections of the string are observed by projecting its shadow upon a screen or recorded by projecting the shadow upon the sensitive film or paper of a photokymograph. An intense light and a system of lenses make projection possible. The string itself is very fine, only 2 or 3 microns in diameter.

The tension of the string is so adjusted that a deflection of 1 cm. on the record represents 1 millivolt. Voltage (horizontal) lines are placed on the record by means of etchings on the lens of the photokymograph. Time lines are recorded by the spokes of a rotating wheel which pass through the field of light at regular intervals and thus cast shadows on the record as it is being made. The wheel is run by a motor controlled by a tuning fork.

The electrical potentials of the heart may be recorded directly by electrodes placed on the exposed heart, or indirectly by electrodes applied to the limbs or the chest. The record in the first instance is an electrogram, in the second an electrocardiogram. An apparatus for making an electrocardiogram is known as an electrocardiograph.

The electrogram is of value experimentally in determining (1) the part of the heart that becomes electrically negative first, that is, the place of origin of the heart beat, (2) the course of the excitatory impulse in the heart, and (3) the rate of travel of the impulse.

The Electrocardiogram. In electrocardiography a "lead" is the connection of two parts of the body by electrodes and wires with the electrocardiograph. In man the three leads adopted by Einthoven have come into general use. They are: right arm and left arm (lead I), right arm and left leg (lead II), left arm and left leg (lead III). In practice electrocardiograms are taken from the three leads in sequence. Additional leads are sometimes used. In animals limb leads similar to those used in man give satisfactory results, although leads derived directly from the chest wall are sometimes used. The normal electrocardiogram shows a number of deflections or waves, some of

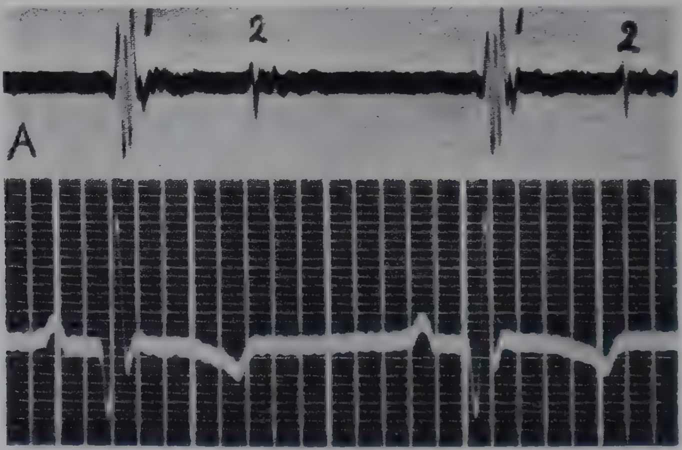

Fig. 21.—Electrocardiogram and phonocardiogram (A) of a normal dog. The Q wave is well defined. The T wave is inverted. The vertical lines are 0.04 sec. apart. The heart rate is 110 beats per minute. In the record of the heart sounds, *1* represents the first sound, *2* the second. Note that the recording paper was run at a faster speed than in Fig. 20. (From Luisada and Mautner, *Experimental Medicine and Surgery,* 1943, 1.)

which are of brief duration while others are longer (Figs. 20, 21, 22). The waves are designated at P, Q, R, S, and T. The P wave is the atrial deflection and is related to atrial systole, although it precedes the mechanical systole by a very brief interval. It is caused by the spread of the wave of excitation from the pacemaker through the atrial musculature. The other waves are related to, and their combined duration is approximately the same as the duration of, ventricular systole. The QRS group is designated as the initial ventricular deflection. It occurs after the passage of the impulse over the A-V bundle and its subendocardial branches. It represents the spread of the impulse in the ventricular musculature, and is a measure of the intraventricular conduction time. Since there is no known practical difference between the wave of excitation and the wave of contraction, the QRS group may be regarded as representing the onset of contraction in the ventricular musculature. The T wave is known as the final deflection. The end of the T wave represents the end of ventricular systole. It indicates the retreat of electrical potential caused by excitation of the ventricular musculature.

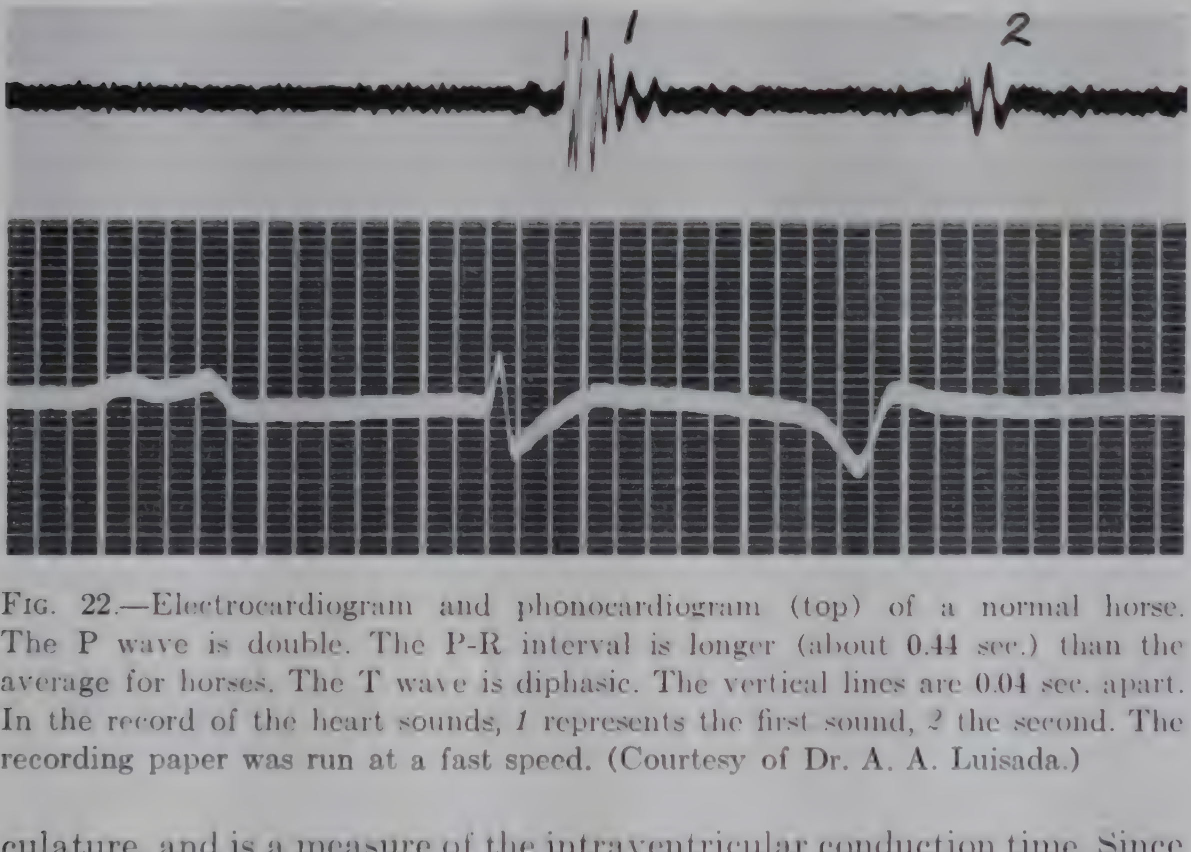

FIG. 22.—Electrocardiogram and phonocardiogram (top) of a normal horse. The P wave is double. The P-R interval is longer (about 0.44 sec.) than the average for horses. The T wave is diphasic. The vertical lines are 0.04 sec. apart. In the record of the heart sounds, *1* represents the first sound, *2* the second. The recording paper was run at a fast speed. (Courtesy of Dr. A. A. Luisada.)

The P-R interval, measured from the beginning of the P wave to the beginning of the QRS complex, represents the time required for the excitation wave to travel from the S-A node to the ramifications of the A-V bundle under the endocardium. It indicates the atrioventricular conduction time.

The Q-T interval indicates approximately the duration of ventricular systole. It indicates accurately the duration of the electrical systole.

The Intervals. In normal dogs Hafkesbring and MacCalmont found the average duration of the P-R interval to be 0.106 sec.; QRS, 0.033 sec. In normal horses Dukes and Batt report average intervals and ranges of variation as follows: P-R, 0.30 sec. (0.20-0.42 sec.); QRS, 0.12 sec. (0.08-0.17 sec.); Q-T, 0.54 sec. (0.46-0.62 sec.) The heart rate was 38 (24-50). In a comprehensive study of the electrocardiogram of dairy cattle, Alfredson and Sykes (1942) found the following average intervals and ranges of variation: P-R, 0.19 sec. (0.10-0.30 sec.); QRS, 0.09 sec. (0.06-0.12 sec.); Q-T, 0.39 sec. (0.29-0.47 sec.).

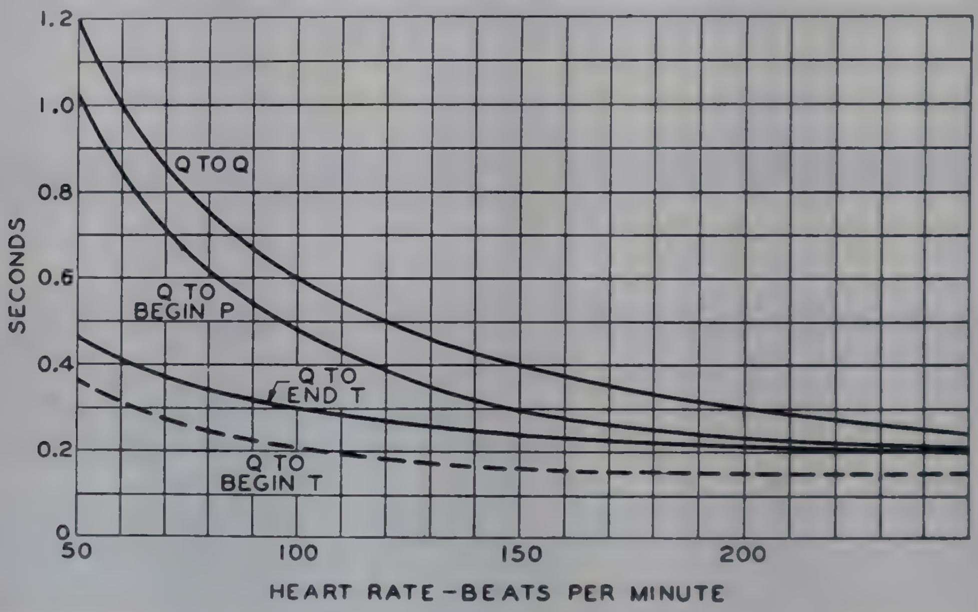

FIG. 23.—Intervals in the electrocardiogram of sheep (average values). Note that as the heart rate increases, the intervals do not change in the same proportion. Any interval (vertical distance) from the lowest horizontal line to the first curve from the top is the duration of a cardiac cycle at the particular heart rate. Electrical systole is the interval (vertical distance) from the lowest horizontal line to the third curve from the top (Q to end of T). The P-R (or P-Q) interval is found between the first and second curves (Q to Q minus Q to beginning of P); the duration of the T wave, between the third and fourth curves (Q to end of T minus Q to beginning of T). (From Ferris, King, Spence, and Williams, *Electrical Engineering*, 1936, 55; copyright—American Institute of Electrical Engineers.)

Intervals in the electrocardiograms of calves have been studied by Barnes, Davis, and McCay. The intervals gradually increased as the animals grew older.

A recent study of Luisada, Weisz, and Hantman contains a great deal of information on the normal electrocardiogram, including the intervals, of many species; and Charton and Minot have reported on the electrocardiogram of horses.

Average intervals in the electrocardiogram of sheep are shown in Fig. 23.

The Deflections. In the horse (limb leads) the P wave may be upward, inverted, diphasic, notched, or double. The R deflection is usually upward. The T wave is usually diphasic, but upward and inverted T waves are common (Dukes and Batt).

In dairy cattle (limb leads) P and T are often diphasic. P is occasionally absent. R is always present in leads II and III. Q is frequently present and is usually small. S is often absent. The form of QRS shows considerable variation. A classification of the electrocardiogram of the cow based on the form of QRS in lead II has been proposed. The amplitude of the different waves varies so much that this factor is of doubtful significance as an index of the nutritive state of the bovine heart. Changes in the form and direction of the T wave in the cow do not have the same significance as in man (Alfredson and Sykes, 1942).

Significance. Electrocardiographic studies have proved to be of value not only in experimental work but in a large number of clinical heart disorders as well. Clinically the electrocardiogram is of value (1) in determining the nature of disturbances in rate and rhythm, that is, the nature of cardiac irregularities, and (2) in detecting diseases of the myocardium. Much more work has been done in the field of clinical electrocardiography of man than of animals. Some clinical aspects of electrocardiography of animals are indicated on p. 132.

APEX BEAT

During systole of the ventricles all diameters of the heart shorten, the ventricles harden, and the heart rotates to the right. The result is that it is more firmly pressed against the chest wall. This increased pressure takes place suddenly and gives rise to a pulsation of the chest wall, often readily visible in man and the dog. This pulsation, known in man as the apex beat, can be registered by means of a receiving tambour, known as a cardiograph, placed over the pulsation and connected by rubber tubing to a recording tambour arranged to write on the smoked paper of a kymograph.

HEART SOUNDS

During the heart beat certain definite sounds are produced. These have long been recognized, but a satisfactory explanation of their cause was not quickly or easily arrived at. They have been studied as an aid to diagnosis for many years. Two distinct sounds can be heard by auscultation of the heart, and occasionally a third sound can be detected in this way. These are designated as the audible heart sounds. The heart sounds may be recorded by various devices. Such records (phonocardiograms) will reveal not only the audible sounds but also at times vibrations that are too feeble to be heard or that lie outside the range of frequency that the ear can detect.

The first sound occurs during ventricular systole and may therefore be designated as the systolic sound. The second occurs at the beginning of ventricular diastole and may be referred to as the diastolic sound. The first sound is longer, of a lower pitch, and of a greater amplitude than the second, which is sharper and more accentuated. The two sounds are fairly well represented by the syllables *lūbb-dŭp*. The sounds can be heard by placing the ear against the thoracic wall over the region of the heart. A phonendoscope or a stethoscope may be employed as an aid to auscultation. The physiological and physical laws governing auscultation have been studied by Rappaport and Sprague (1941).

The first heart sound is usually stated to be due to a combination of two factors, valvular and muscular. When the ventricles contract the intraventricular pressure is suddenly elevated; this completes the closure of the A-V valves. The flaps of the valves and the chordae tendineae are put under tension owing to the high pressure of the blood in the ventricles, and so are caused to vibrate and produce sound. It is commonly stated that the vibration of the contracting ventricular muscle fibers also produces sound and that this is blended with the valvular element to cause the first heart sound. Experiments by Dock and by Eckstein minimize the importance of the muscular element in the production of the first heart sound; but the older view that the contracting ventricular muscle contributes directly to the causation of the first sound is reaffirmed by experiments of Smith, Kountz, and Gilson. The frequency of the vibrations of the first heart sound (man) is some 30 to 45 per second.

The second heart sound occurs immediately after the closure of the aortic and pulmonary valves, and it is generally agreed that their after-vibration produces the sound. This conclusion is based largely on the fact that when the valves are prevented from closing no second sound occurs. The frequency of the vibrations that make up the second heart sound (man) is about 50 to 70 per second.

A third heart sound is occasionally audible in man. It is feeble and is believed to be related to the flow of blood into the ventricle during the phase of rapid filling (Wiggers, 1944). An audible third heart sound in animals is probably of infrequent occurrence, if it occurs normally at all. However, a third heart sound has been detected in phonocardiograms of horses. It is present only exceptionally (Luisada, Weisz, and Hantman).

The contracting atrium may produce sound but it is usually obscured by the first heart sound. In heart-block (p. 133) the atrial sound may be audible. Heart-block with audible atrial sound has been observed in horses (Dukes, Batt, Luisada).

Phonocardiograms. Graphic records of the heart sounds may be made in several ways. In one method a stethoscope is placed over the region of the heart and connected with a microphone in a primary circuit. A string galvanometer is placed in the secondary circuit. The string of the galvanometer is deflected by the sounds of the heart and the deflections are recorded on a moving photographic surface.

Another method makes use of a microphone, vacuum-tube amplifier, and galvanometer (Rappaport and Sprague, 1942) by means of which the amplified electrical changes are detected. The deflections of the galvanometer are recorded on a moving light-sensitive surface.

The heart sounds may be recorded directly (Wiggers, 1944). They are picked up by a funnellike device applied to the chest wall and are then transmitted by a rubber tube to a little chamber across the open face of which a delicate rubber membrane is stretched. Adhering to the rubber film is a small mirror which moves with the deflections of the film. A band of light from a suitable light source is transmitted to the mirror which reflects it onto a photosensitive surface.

Graphic records of normal heart sounds are included in Figs. 21 and 22.

Abnormal heart sounds are designated as murmurs or bruits. They may modify or completely replace the ordinary heart sounds. They give valuable information to the clinician about the condition of the heart valves and orifices. Phonocardiograms showing abnormal heart sounds are seen in Figs. 24 and 25.

Graphic records of the heart sounds of animals are presented in a recent study by Luisada, Weisz, and Hantman. A phonocardiographic study of the heart sounds of horses has been made by Charton, Minot, and Bressou.

CARDIAC CYCLE

By a cardiac cycle is meant a complete heart beat. Some of the pioneer experimental work on this subject was done on the horse, ass, and mule by Chauveau and Marey, using both direct observations of open-chest subjects and the graphic method. Modern methods of study of the cardiac cycle include the optical registration of pressure changes in the heart chambers and the great arteries near the heart. Tlectrocardiograms, phonocardiograms, and records of volume changes of the ventricle are also used.

From such records the events of a cardiac cycle can be deduced. Semidiagrammatic records (from below upward) of the heart sounds, the electrical changes, left intra-atrial pressure, left intraventricular pressure, and aortic pressure are assembled in Fig. 26. The pressure changes occurring in the right atrium, right ventricle, and pulmonary artery are qualitatively similar to those occurring in the corresponding chambers on the left side, but the pressures that develop in the right ventricle and the pulmonary artery are much lower than the pressures in the left ventricle and the aorta.

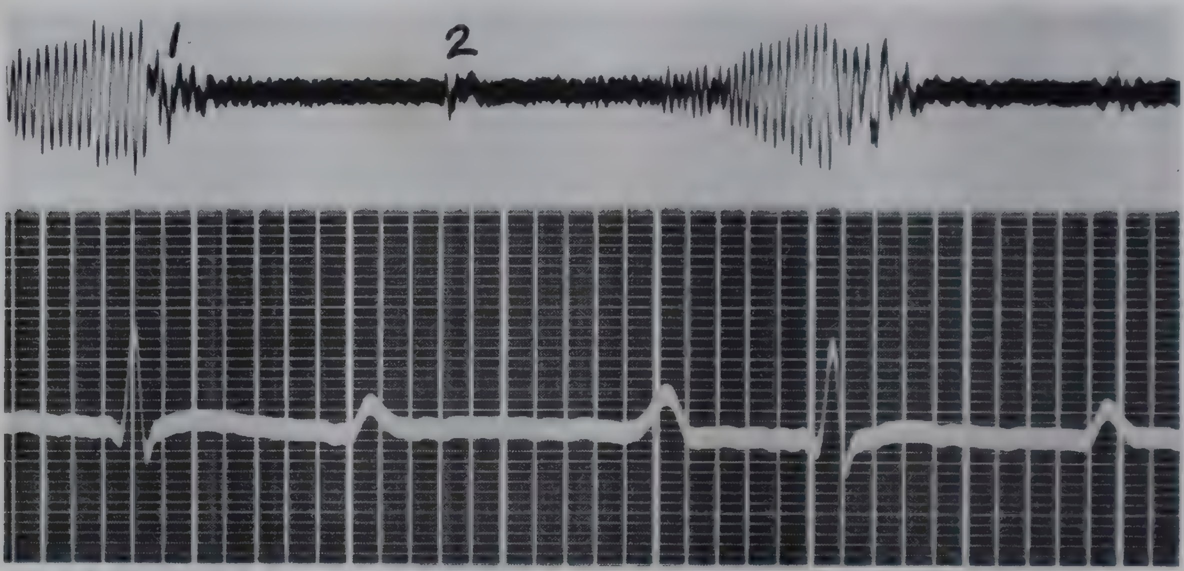

FIG. 24.—Phonocardiogram (top) and electrocardiogram of a horse. Shows a presystolic musical sound. The ordinary heart sounds are indicated by *1* and *2*. The vertical lines are 0.04 sec. apart. (Courtesy of Dr. A. A. Luisada.)

Starting at the left of the figure, one sees an elevation of intra-atrial pressure (broken line) and a corresponding elevation of intraventricular pressure (continuous line). The pressure changes are caused by atrial contraction. The similarity of the curves indicates that the A-V valve is open and that the two cavities are in free communication with each other. The start of the P wave of the electrocardiogram precedes the start of atrial contraction by a very brief interval. This is due partly to the slight actual lag between the electrical change and the contraction but largely to the fact that the contraction does not develop a measurable pressure change until the excitatory process, of which the electrical change is a manifestation, has spread for some distance from the pacemaker. Atrial relaxation now sets in and intra-atrial pressure falls. It may actually drop slightly below that in the ventricle, for as the atrium relaxes the A-V valves tend to close. This prevents a corresponding fall of pressure in the ventricle.

Ventricular contraction now begins and intraventricular pressure rises sharply. The measurable rise follows by a very brief interval the beginning of the initial ventricular deflection (QRS) of the electrocardiogram. Intraventricular pressure soon exceeds intra-atrial pressure and the A-V valve is firmly closed (A.V.C.). The valve bulges somewhat into the atrium, but it is prevented from everting into the upper chamber by the tugging action of the contracting ventricular muscle on the chordae tendineae. The bulging of the valve into the atrium causes intra-atrial pressure to rise slightly. As previously indicated, the vibration of the A-V valves and the chordae, incident to the firm closure of the valves, is the principal cause of the first heart sound. Contraction of the ventricle results in a downward movement of the base of the ventricle. This lengthens the atria, and the intra-atrial pressure drops. During the remainder of ventricular systole, atrial pressure rises because of the continuous inflow of blood from the veins. The rise continues until intraventricular pressure falls below the pressure in the atrium, whereupon the A-V valve opens (A.V.O.) and blood flows freely from the upper chambers into the lower. The atrium and ventricle now being in free communication with each other through the open A-V valve, their pressures will rise together, as blood continues to flow into both chambers, until the next atrial contraction.

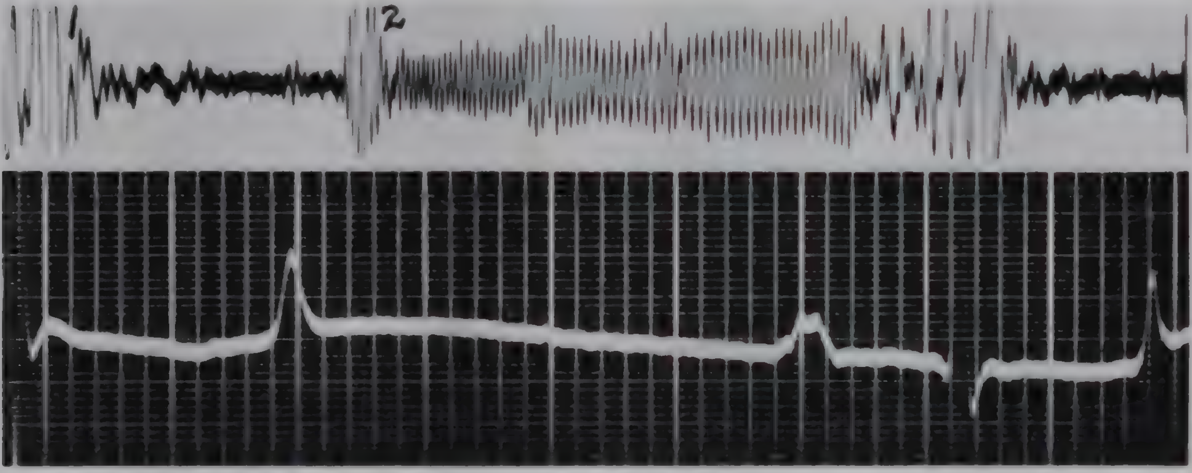

FIG. 25.—Phonocardiogram (top) and electrocardiogram of a horse. Shows a diastolic musical sound. The ordinary sounds are indicated by *1* and *2*. The vertical lines are 0.04 sec. apart. (Courtesy of Dr. A. A. Luisada.)

Returning to a consideration of intraventricular pressure, and comparing it to aortic pressure, one observes that it continues to rise very sharply until it exceeds the pressure in the aorta, whereupon the aortic valve opens (S.L.O.) and the aortic pressure parallels, more or less closely, the intraventricular pressure. In the brief interval (about 0.04 sec. in Fig. 26) between the closure of the A-V valve and the opening of the aortic valve, the ventricular muscle fibers are

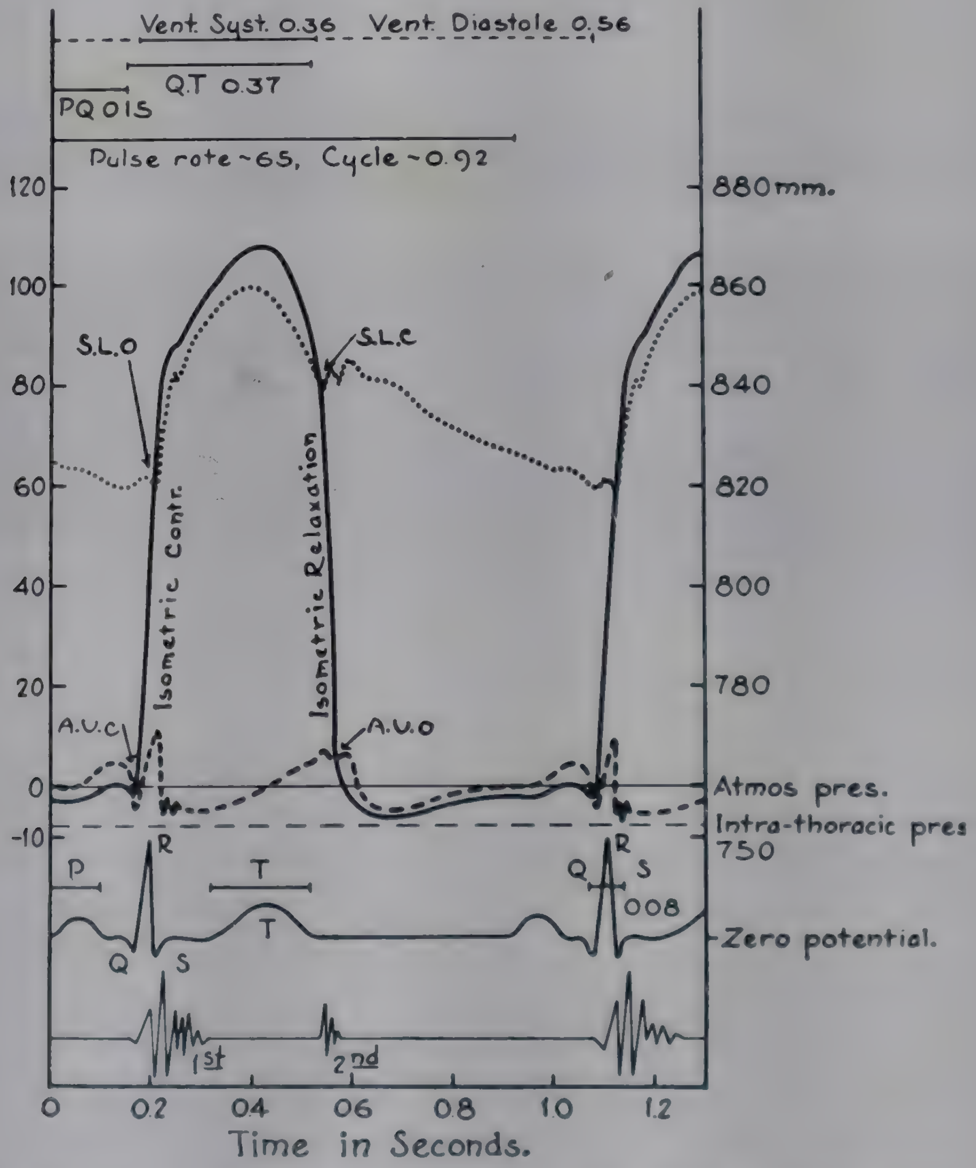

FIG. 26.—Principal events of a cardiac cycle. From below upward: heart sounds, electrocardiogram, left intra-atrial pressure (broken line), left intraventricular pressure, and aortic pressure (dotted line). Pulse rate, 65. The left vertical axis shows pressure (mm. Hg) relative to atmospheric pressure; the right vertical axis shows absolute pressure. Note that the Q wave of the electrocardiogram begins slightly before the intraventricular pressure rises. The values for the intervals are illustrative only. A.V.C. and A.V.O. indicate closing and opening of the A-V valves. S.L.O. and S.L.C. indicate opening and closing of the semilunar valves. (From Macleod's *Physiology in Modern Medicine*, The C. V. Mosby Company.)

contracting but not shortening, that is, they are contracting isometrically. This phase is spoken of as the *isometric contraction phase* of ventricular systole. During this time the ventricle is a closed cavity. Ejection of blood into the aorta is at first *maximum* and the pressures continue to rise. Ejection is later *reduced* and the pressures fall. Ventricular relaxation now begins and a sharp drop in intraventricular and aortic pressures results. This marks the beginning of *ventricular diastole*. It follows by a slight interval the end of the T wave of the electrocardiogram. The fall of aortic pressure is checked by the closure of the aortic valve (S.L.C.). The second heart sound then follows. The very brief interval from the beginning of diastole to closure of the aortic valve is known as the *protodiastolic phase*. Tension in the ventricular musculature continues to diminish, but the volume of the ventricle remains unchanged until the pressure in the ventricle has fallen low enough to permit opening of the A-V valve (A.V.O.). The time elapsing between closure of the semilunar valve and opening of the A-V valve is known as the *isometric relaxation phase* of ventricular systole. There is now a *phase of rapid filling* of the ventricle by the blood stored in the atrium and that flowing in from the great veins. During this phase ventricular volume rapidly increases. This phase is followed by a *phase of diastasis,* the length of which is related to the duration of the cardiac cycle. If the heart rate is increased and the cycle therefore shortened, the phase of diastasis is shortened. The phase of rapid filling is not much affected as the pulse rate increases. This means that ventricular filling is still efficient. *Atrial systole* is the last phase of ventricular diastole.

The average duration of the different phases of the cardiac cycle in the dog with a pulse rate of 75 is shown in the accompanying table.

AVERAGE DURATION OF PHASES OF CARDIAC CYCLE OF DOG (PULSE RATE 75)

Isometric contraction	0.05 sec.
Maximum ejection	0.12 sec.
Reduced ejection	0.10 sec.
Systole	0.27 sec.
Protodiastole	0.02 sec.
Isometric relaxation	0.05 sec.
Rapid filling	0.06 sec.
Diastasis	0.29 sec.
Atrial systole	0.11 sec.
Diastole	0.53 sec.

(Data from Wiggers.)

Several features of the cardiac cycle of the horse are shown in Figs. 27 and 28.

THE CARDIAC OUTPUT AND THE VOLUME OF THE CIRCULATION

The left side of the heart pumps blood through the body and into the right side, whereas the latter pumps blood through the lungs and into the left side. Obviously the inflow and outflow from the two sides of the heart could not be different except for a few beats; otherwise stasis of the circulation at some point would result. The ventricular output can be measured rather directly, in the laboratory mammals, by recording the volume changes of the ventricles inclosed in a cardiometer. The thorax is opened and artificial respiration is provided; the ventricular portion of the heart is now inclosed in a cardiometer. One form of this is a globular chamber with a side tube, and a large opening across which a thin rubber membrane is stretched and tied. The ventricles are introduced into the cardiometer through an opening in the rubber membrane, the edges of which fit air-tight around the heart at the atrioventricular junction. The side tube of the cardiometer is then connected by rubber tubing with a recorder arranged to write on a kymograph. Systole results in an increase in the space in the cardiometer, and the lever of the recorder moves upward or downward depending on the arrangement of the recorder. Diastole results in a decrease of the space and the lever moves in the opposite direction. In this way a tracing of the volume changes of the ventricle can be made. Optical recording may be used, in which case the volume changes

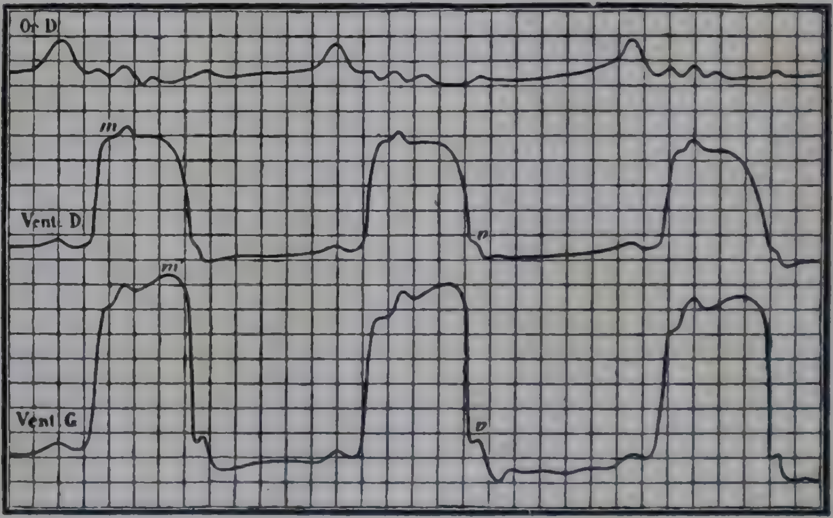

FIG. 27.—Simultaneous tracings of pressure in the right atrium (Or. D.), the right ventricle (Vent D.), and the left ventricle (Vent. G.) of horse. (Marey, 1881.)

could be transmitted to a small chamber the open face of which is covered with a rubber membrane to which a tiny mirror is attached. The mirror moves with the movements of the membrane. A band of light is transmitted to the mirror which reflects the light onto a moving light-sensitive surface (paper or film) in a photokymograph.

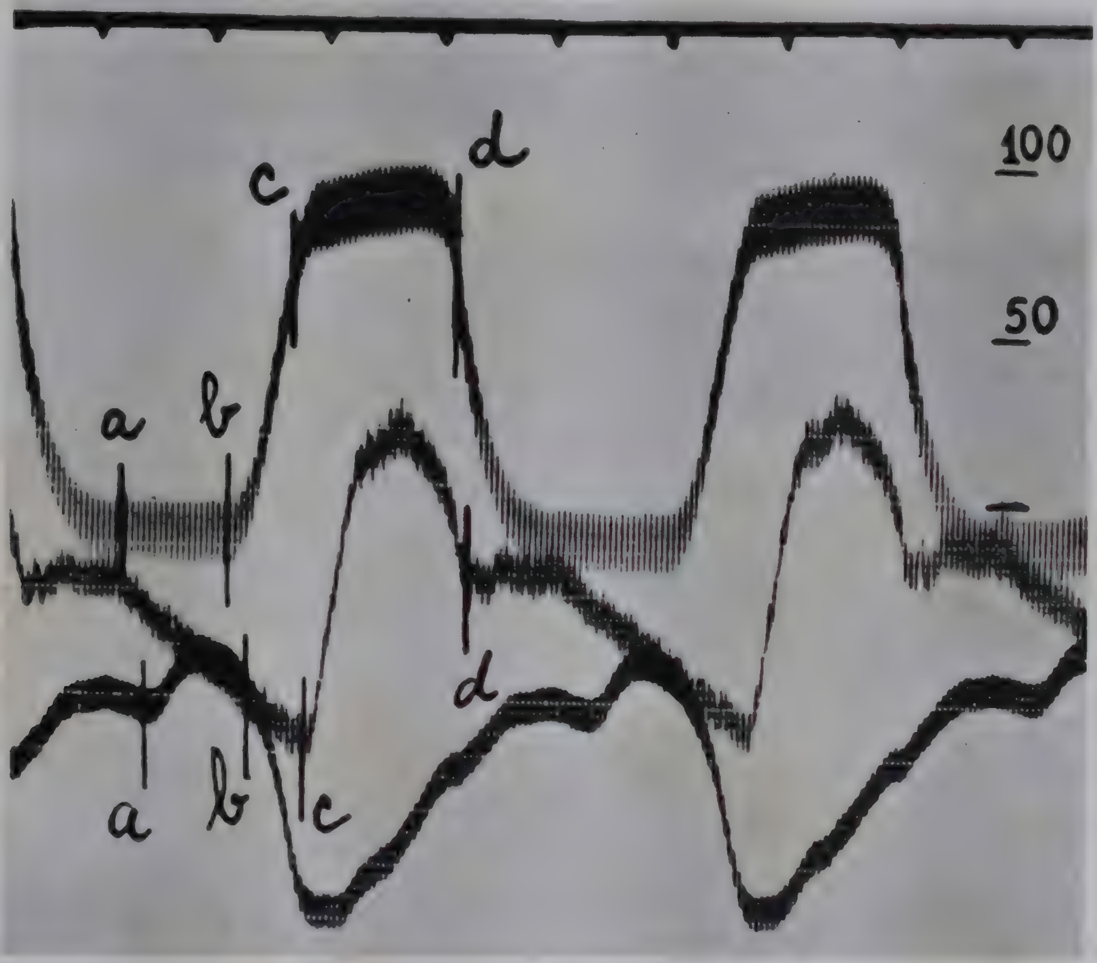

FIG. 28.—Optically recorded pressure changes in left ventricle (top tracing), aorta (middle tracing), and right atrium (bottom tracing) of a horse. Time intervals, 0.2 sec. Heart rate, 80 beats per minute. The vertical lines indicate synchronous points on the tracings. The delay in the two lower records was caused by the length of the tubes from the aorta and atrium to the recording capsules. a-b, Atrial contraction; b-c, isometric contraction phase of ventricular systole; c-d, ejection phase. (From Houssay, Orias, and Giusti, *Journal de Physiologie et de Pathologie générale,* 1936, 34.)

Absolute values derived as just indicated do not necessarily represent the ventricular output in the normal intact animal, but they are of value for purposes of comparison under different experimental conditions.

The cardiac output in man and animals under normal conditions of rest and work can be estimated indirectly. The output of each ventricle per beat is termed the *stroke volume* of the heart, the systolic discharge, or the pulse volume, while the output of each ventricle per minute is termed the *minute volume of the circulation*, or the cardiac output per minute. It is evident that $\frac{\text{minute volume}}{\text{pulse rate}} = \text{stroke volume}$. Therefore if the minute volume could be found it would be a simple matter to calculate the stroke volume. Several methods of estimating the minute volume are in use. One method—the Fick procedure—involves a determination of the difference between the oxygen content of arterial and venous bloods and a determination of the oxygen consumption of the animal per minute. In animals samples of arterial and mixed venous bloods can be obtained by puncture of the left and the right ventricle, respectively, through the chest wall, without greatly inconveniencing the animal or altering its normal condition.[1] Samples of arterial blood may also be obtained by arterial puncture and samples of mixed venous blood by catheterization of the right atrium via a jugular vein. The blood samples are analyzed for their oxygen content. It is found of course that the amount of oxygen in venous blood is less than that in arterial blood because of the using of oxygen by the tissues. The difference represents the *arteriovenous oxygen difference* and is expressed in per cent by volume. It is the number of volumes (cc.) of oxygen removed by the tissues from every 100 volumes (cc.) of blood pumped from the left ventricle. The second factor required, the oxygen consumption of the animal per minute, can be measured by methods described in Chapter XXI.

Knowing the arteriovenous oxygen difference and the oxygen consumption per minute, the minute volume of the circulation can be calculated by a simple procedure. An example will serve to make this clear. Barcroft and co-workers found in resting goats (mean weight, 23.7 kg.) that the mean oxygen consumption was 176 cc. per animal per minute and that the mean arteriovenous oxygen difference was 5.83 cc. per 100 cc. of blood. The minute volume of the circulation (x) was therefore:

$$5.83:100 :: 176:x$$
$$x = 3018 \text{ cc.}$$

In the report of this experiment the pulse rate of the animals is not given, but in order to complete the illustration, it may be assumed that it averaged 70 per minute. The average stroke volume would therefore be

$$\frac{3018}{70} = 43 \text{ cc.}$$

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[1] Serious results may follow puncture of a coronary artery.

Zuntz and Hagemann found the minute volume of the circulation of a resting, 342-kg. horse to be 24,008 cc. If a pulse rate of 40 is assumed, the stroke volume becomes 600 cc.

Clark (1927) gives the accompanying estimates of the minute volume of the circulation in various animals and man at rest. The calculations are based on a known oxygen consumption (shown in the table) for each animal and an assumed arteriovenous oxygen difference of 5 cc. If estimated pulse rates are supplied, the average stroke volume can be calculated in each instance, as is done in the table.

MINUTE VOLUME OF CIRCULATION AND STROKE VOLUME OF HEART

Animal	Body Weight	Oxygen Consumption (a)	Minute Volume $\frac{a}{5} \times 100$	Pulse Rate	Stroke Volume
	kg.	*cc./min.*	*cc.*		*cc.*
Ox	500	1740	34,800	60	580
Horse	500	1450	29,000	34	852
Man	70	253.5	5,070	70	72
Sheep	50	199	3,980	75	53
Dog	10	72.5	1,450	100	14

Another method of estimating the minute volume of the circulation is based upon a determination of the arteriovenous CO_2 difference and the CO_2 output of the animal. The principle is the same as in the preceding method.

Knowing the minute volume of the circulation and the total volume of blood in the body (Chapter II), one can estimate the time required to effect a complete circulation of the blood. Thus if a 500-kg. cow has a total blood volume of 36,000 cc. and a minute volume of the circulation of 35,000 cc., it is evident that the total circulation time would be

$$\frac{\text{Total volume}}{\text{Minute volume}} = \frac{36{,}000 \text{ cc.}}{35{,}000 \text{ cc./min.}} = 1.03 \text{ min.}$$

This value is in fair agreement with measurements of the circulation time in cattle made by Turner and Herman. They injected a fluorescent substance (fluorescein) into the mammary vein on one side and determined, by collection of blood at 5-second intervals, the time required for it to appear in the mammary vein of the opposite side. The average time was 52 seconds.

Examination of the figures in the table reveals that in every instance the quotient $\frac{\text{stroke volume (cc.)}}{\text{body weight (kg.)}}$ is more than 1 but less than 2. This number, the output of the ventricle in cubic centimeters per beat per kilogram of body weight, Henderson designated as the *stroke index*. He expressed the view that in all athletic mammals it is equal to 1.4 to 1.8 cc. at rest.

Variations in the Minute Volume with Work. The real function of the circulation is to move blood through the capillaries in order to meet the metabolic requirements of the tissues. The nutritive substance whose absence or deficiency causes the quickest and most profound tissue derangement is oxygen. During muscular work the oxygen requirements of the muscles may be increased many times. Halliburton found that actively contracting skeletal muscle may use 13 times as much oxygen per minute as during rest. Brief reflection shows that the increased demands for oxygen may be met by an increase in the efficiency of utilization of the oxygen in arterial blood, that is, by an increase in the arteriovenous oxygen difference, or by an increase in the minute volume of the circulation, or both. That the first of these may happen is undoubted. It is referred to again on p. 215. That the second factor, the increase in the minute volume of the circulation, happens is proved by experiments on animals and man. Zuntz and Hagemann in their extensive work on the horse found that the minute volume of the circulation of an animal weighing 342 kg. increased from 24,008 cc. at rest to 59,511 cc. during work. In man a ninefold increase as a result of severe exercise has been observed.

An increase in the minute volume of the circulation may be brought about by an increase in the heart rate or the stroke volume or both. That the heart rate increases during muscular work is well known. The increase is effected largely through the nervous system and is considered in Chapter V. That the stroke volume also may be increased there can be no doubt. Such an increase is due in part to nervous influences, which receive attention in Chapter V. Yet it is due in part to some intrinsic power of the heart to regulate itself, which will be considered now.

Intrinsic Regulation of the Cardiac Output. That there may be increases or decreases in the stroke volume of the heart quite independent of nervous control is indicated by experiments in which the heart, completely isolated from nervous connections, is arranged in such a way that the rate of filling of the right atrium can be varied at will and the changes in volume of the ventricles recorded. Such an arrangement is known as the heart-lung preparation (Knowlton and Starling), a diagrammatic representation of which is shown in Fig. 29.

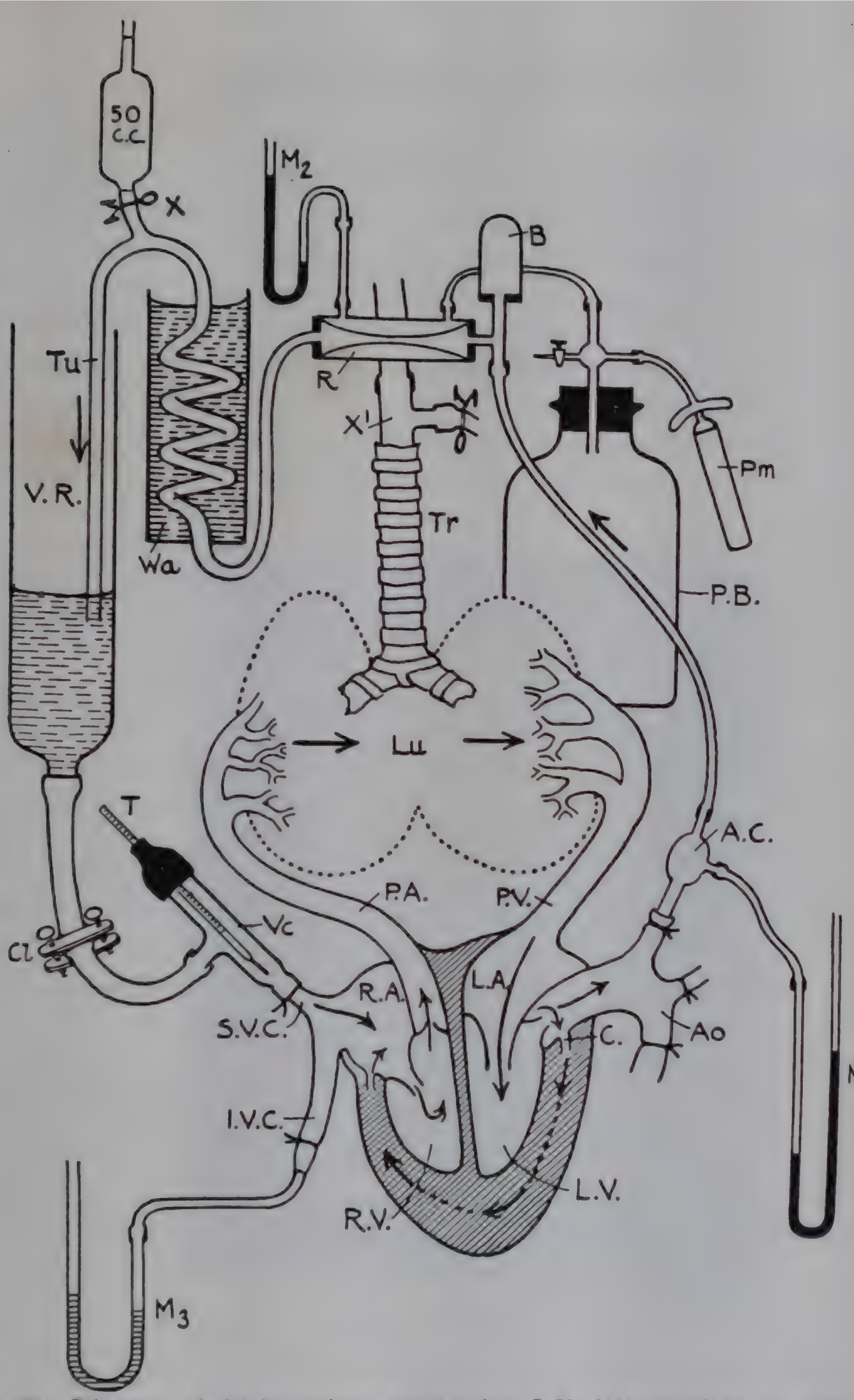

FIG. 29.—Diagram of the heart-lung preparation. L.V., left ventricle; C., coronary circulation; Ao, aorta; A.C., arterial cannula; M_1, manometer for registering arterial pressure; P.B., pressure bottle; Pm, pump; B, air chamber; R, resistance, consisting of a thin-walled rubber tube inclosed in a glass jacket; Wa, warming arrangement; V.R., venous reservoir; Cl, adjustable clamp; Vc, venous cannula; S.V.C., anterior vena cava; I.V.C., posterior vena cava; R.A., right atrium; R.V., right ventricle; L.A., left atrium; L.V., left ventricle; M_3, manometer for registering venous pressure; P.A., pulmonary artery; Lu, lungs; P.V., pulmonary veins; Tr, trachea; X′, tracheal cannula. The arrows indicate the direction of blood flow. (From Starling's *Principles of Human Physiology*)

The thorax of the animal is opened, and the aorta and all its branches, except the brachiocephalic artery, are ligated. A three-way cannula is inserted into the brachiocephalic artery; a manometer, for recording arterial pressure, and a rubber tube are connected to the cannula. This rubber tube is then connected with a thin-walled rubber tube inclosed in a glass jacket. The air pressure on the interior of the jacket can be altered, thus varying the resistance to the flow of blood through the thin-walled rubber tube. Another tube runs from the thin-walled rubber tube to a warming apparatus, and this in turn is connected with a venous reservoir, into which defibrinated or heparinized blood is placed. The venous reservoir communicates with a cannula in the anterior vena cava. The posterior vena cava is connected to a manometer for recording venous pressure. The pulmonary circuit is left undisturbed, and the lungs are ventilated by artificial respiration. The preparation may be removed from the body. Furthermore, it may be inclosed in a large glass jacket, the pressure on the inside of which can be lowered in imitation of the negative pressure of the thorax. As a result of these procedures the circulation of blood is as follows: From the left ventricle through the variable resistance and the warmer into the venous reservoir; from the venous reservoir into the right atrium and thence into the right ventricle; from the right ventricle through the lungs and back to the left atrium. The coronary circulation is undisturbed, and blood coming from the coronary capillaries is the only venous blood in the circulation. It mixes in the right atrium with blood from the venous reservoir. Aeration takes place in the lungs. Anemia of the central nervous system abolishes nervous control.

The heart-lung preparation possesses the following advantages: (1) The influence of the nervous system on the heart and the blood vessels is entirely removed. (2) The heart rate remains constant. (3) The arterial resistance, and hence the arterial pressure, can be controlled. (4) The cardiac output in a given time can be measured directly at the venous reservoir. (5) The temperature of the blood can be controlled. (6) The rate of venous inflow can be varied.

From the preparation graphic records may be made of volume changes in the heart, of arterial blood pressure, of the volume of the circulation, and of venous blood pressure. If desired, the blood flow in the coronary circuit can be measured and recorded, after inserting a cannula into the coronary sinus.

By opening the clamp between the venous reservoir and the right atrium the rate of venous inflow is augmented, and the output of the heart must increase correspondingly or the pressure in the right atrium and great veins must rise greatly. Tracings show that the venous pressure increases, but not very much unless the inflow is excessive, whereas cardiometer tracings indicate an augmented output, due to an increase in the stroke volume, that is, to an increase in the amplitude of the heart beat (Fig. 30). The explanation of how it is possible for the heart to accommodate this increased venous return and to eject an increased amount of blood into the arteries at every systole is afforded by Starling's *law of the heart*, which states that the energy liberated by the heart muscle fibers upon contraction varies directly with the length of the fibers—that is, the volume of the heart—at the end of diastole.

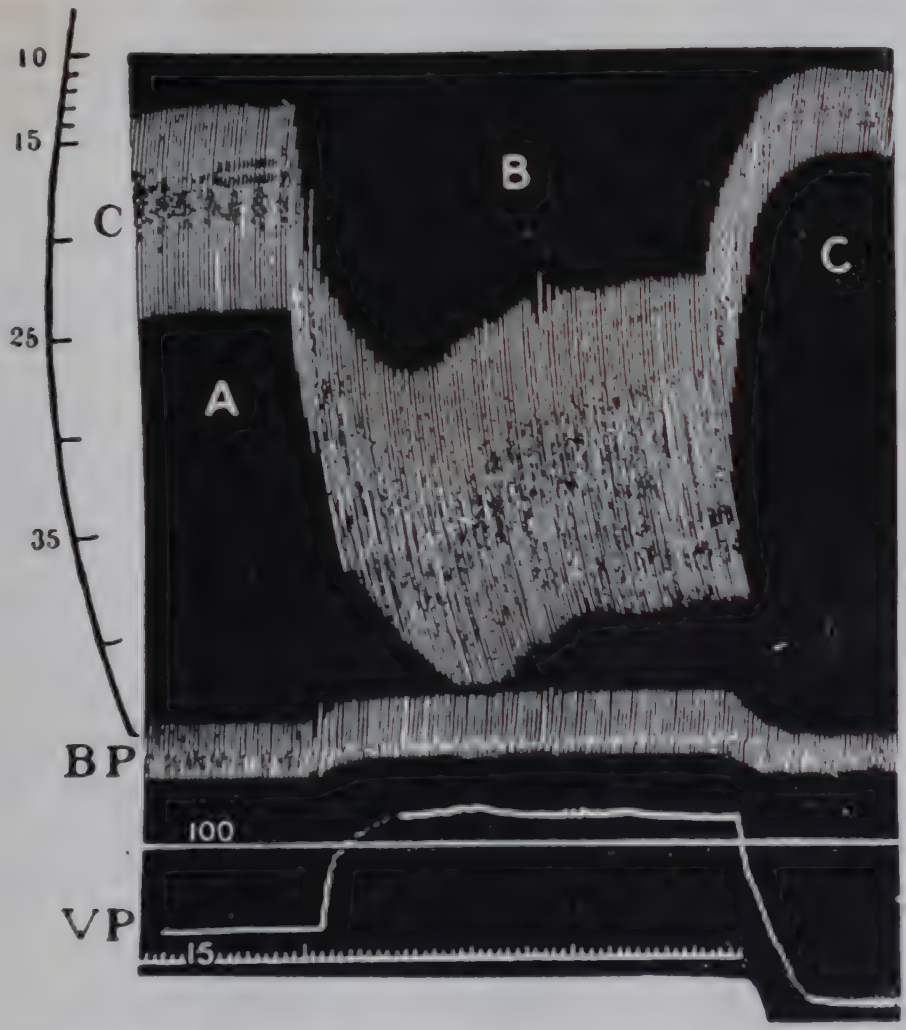

FIG. 30.—Showing the effect of variations in venous inflow on the volume and output of the heart. C, cardiometer record (upstroke is contraction); BP, arterial pressure; VP, venous pressure. The volume changes (in cubic centimeters) may be determined by reference to the scale at the left of the tracing.

	A	B	C
Arterial pressure (mm. Hg)	124	130	124
Venous pressure (mm. H_2O)	95	145	55
Output of heart (cc./10 sec.)	86	140	33

(From Starling's *Principles of Human Physiology*.)

The amount of blood expelled from each ventricle during systole is determined, therefore, by the extent to which the ventricle is filled at the end of diastole, and this is determined by the rate of venous inflow. Wiggers states that "the greater systolic discharge is accomplished largely by a greater velocity of ejection but to some extent also by lengthening of the period of systolic discharge."

This ability to contract with greater force when stretched, within limits, is true not only of heart muscle but of other muscle tissue as well. It is probably explained by the greater surface of the stretched fiber and hence the greater rate of chemical change (metabolism) taking place.

As previously stated, increased venous return to the heart is not accommodated solely by an increase in the stroke volume, but often also by a simultaneous increase in the heart rate. The heart-lung experiment, in which the pulse rate is constant, proves that the stroke volume can be augmented but does not prove that the rate of the heart in the normal animal can not also be increased when the venous return is increased. Indeed, it is common knowledge that the heart rate can be greatly increased.

Another important adjustment on the part of the heart has been studied by use of the heart-lung preparation. This adjustment prevents a decrease in the output of the ventricle, except for a few beats, when the arterial pressure is elevated. As a result of the increase in arterial pressure, the ventricle discharges less blood for a few beats, in consequence of which the volume of the ventricle must increase, for the volume of blood entering the heart from the venous reservoir remains unchanged. This increase in ventricular volume results in lengthened heart muscle fibers which, according to the law of the heart, expend more energy in contracting. Thus in a short while the ventricle is discharging the same amount of blood as formerly, in spite of the elevation of arterial pressure.

THE WORK AND EFFICIENCY OF THE HEART

Since most of the mechanical energy of the heart beat is used in expelling blood into the arteries against pressure, the approximate amount of the work of the heart per beat can be calculated by use of the expression

$$W = QR$$

where W is the work, Q the volume of blood expelled, and R the mean arterial resistance in meters of blood (mean arterial pressure in millimeters of mercury × 0.013, mercury being about 13 times as heavy as blood).

However, not all the mechanical energy of the heart beat is used in overcoming arterial pressure; a part is used in giving velocity (kinetic energy) to the blood, especially when the minute volume of the circulation is increased. It follows, therefore, that the expression given above is inadequate, especially during muscular effort. It must contain a velocity factor. At rest the simple equation probably accounts for 95 per cent or more of the mechanical work done, whereas during marked exercise the velocity factor may be responsible for 20 per cent or more of the total work.

Expressions which contain a velocity factor and which permit the calculation of the approximate amount of work done by one or both ventricles, respectively, are the following:

$$W = QR + \frac{mV^2}{2g} \text{ for one ventricle, or}$$

$$W = \frac{7}{6}QR + \frac{mV^2}{g} \text{ for both ventricles,}$$

in which Q is the volume of blood expelled during systole, R the resistance or mean arterial pressure, m the weight of blood ejected, V the average velocity at which it is ejected, and g the acceleration due to gravity, a constant amounting to 9.8 meters per second per second. If Q is in liters, R in meters of blood, m in kilograms, and V in meters per second, W will be in kilogram-meters of work during the time under consideration. The pressure in the right ventricle is about one-sixth that in the left. Therefore QR is multiplied by 7/6 in order to obtain the value of QR for both ventricles. R in this case is the mean aortic pressure.

An example of the work done per minute by the heart of a cow may be given. A mean aortic pressure of 120 mm. Hg, a minute volume of 35 liters, and an average aortic velocity during systole of 1.5 meters per second will be assumed.

$$W = \frac{7}{6}QR + \frac{mV^2}{g}$$

$$= \frac{7(35 \times 120 \times 0.013)}{6} + \frac{35 \times 1.06 \times 2.25}{9.8}$$

$$= 63.7 + 8.5 = 72.2 \text{ kilogram-meters per minute.}$$

By the efficiency of an engine is meant the percentage of the total energy expenditure that is converted into mechanical work. The efficiency of muscle is stated similarly. The efficiency of heart muscle has been determined on isolated, working hearts by measuring the oxygen consumption and calculating the mechanical work done in pumping blood. From the oxygen consumption over a given time the total energy exchange as calories can be calculated (1 liter O_2 = approx. 4800 cal.) The mechanical work can be changed into equivalent calories (1 kilogram-meter = 2.34 cal.).

$$\text{Efficiency} = \frac{\text{Caloric equivalent of mechanical work}}{\text{Total energy exchange (calories)}} \times 100.$$

Experiments show, on the whole, that the efficiency of heart muscle is about the same as that of skeletal muscle, 20 to 25 per cent.

THE CORONARY CIRCULATION

Heart muscle is supplied with blood by the two coronary arteries. These break up into numerous capillaries in the heart wall, thus insuring an abundant blood supply to each muscle fiber. The capillaries by their union form ultimately the coronary veins, which empty into the coronary sinus of the right atrium. Anatomical studies have shown that in the heart musculature of mammals there are, in addition to the coronary vessels, several types of vessels which establish communication between the coronary capillaries and the chambers of the heart. To what extent these vessels are concerned in the normal nutrition of the heart is at present uncertain, but that they may be of importance under certain pathological conditions of the coronary vessels is probable (Wiggers).

Occlusion of a coronary artery, as by ligation or by thrombosis, results in sudden death from ventricular fibrillation (p. 134). Occlusion of a large branch may or may not cause death, depending on the size of the vessel occluded and other factors. If death does not occur, varying degrees of functional impairment of the heart will result. The effect on intercoronary collateral circulation of experimental narrowing of a coronary artery has been studied in pigs by Blumgart and co-workers.

It is now known that the orifices of the coronary arteries are in free communication with the aorta during both ventricular systole and diastole. This is contrary to an earlier belief that the cusps of the aortic valve close the orifices during systole. That the present view is correct is shown by the fact that the pressure variations in the coronary arteries parallel those in the aorta. In short, blood pressure in the coronary arteries behaves toward aortic pressure in much the same way as does blood pressure in arteries of organs and tissues in general.

The left coronary artery of the dog is estimated to distribute 80 per cent of the total coronary blood flow. More than half of the flow in the left artery is distributed through its circumflex branch. Essex and co-workers have made studies on the blood flow in the circumflex branch of the left coronary artery of the dog under different conditions. The thermostromuhr method (p. 145) was used. During exercise the maximum increase over the control rate of flow was fourfold: blood flow during the control period, 60 cc. per minute; during work on a treadmill, 250 cc. per minute. Changes in coronary blood flow during exercise were more accurately reflected by changes in the pulse rate than by changes in the blood pressure (Fig. 31). Adrenaline caused a distinct increase of short duration. In some experiments the increase was as much as four or five times the resting value. Thyroxine caused a prolonged increase in coronary flow, but the effect did not come on until more than 24 hours after the injection of the hormone. During digestion the coronary blood flow was increased similarly to the increase observed in other arteries of the body.

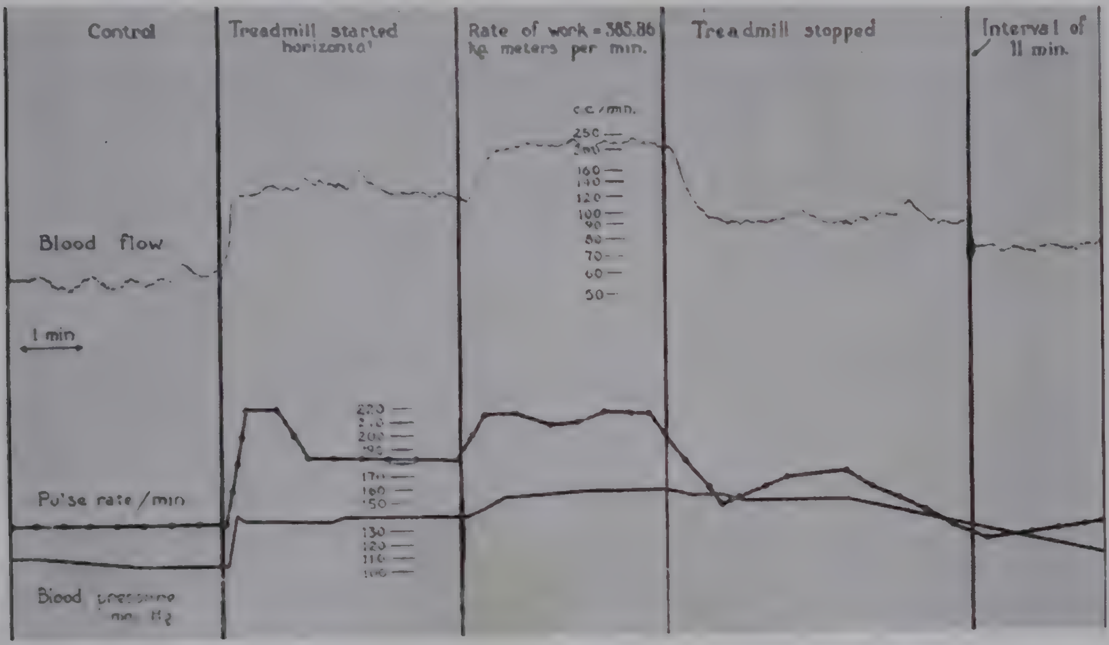

FIG. 31.—Simultaneous records of blood flow (thermostromuhr method) in circumflex branch of left coronary artery, pulse rate, and mean blood pressure of a dog before, during, and after exercise at two different rates on a treadmill. Note that changes in pulse rate reflect changes in coronary blood flow more accurately than do changes in blood pressure. (From Essex, Herrick, Baldes, and Mann, *American Journal of Physiology*, 1939, 125.)

Much work has been done on the problem of the coronary blood flow during systole of the heart. Some results have tended to show that the flow is reduced or stopped during systole, while other work indicates acceleration of flow. Experiments of Green, Gregg, and Wiggers reveal that the myocardium receives a very significant supply of blood during contraction, nearly as much in fact as during a similar period of diastole. However, the total flow during diastole is much greater than during systole because of the greater length of diastole.

The coronary circulation is the subject of a recent review by Gregg.

The nervous regulation of the coronary vessels is discussed in another place (p. 178).

THE PERICARDIUM

The physiological significance of the pericardium is not well understood. Among the several functions that have been attributed to it (Wiggers and Green), the following may be mentioned: (1) It protects the heart against overdilatation. (2) It provides smooth surfaces for the heart's action. (3) It holds the heart in a relatively fixed position. (4) It assists in relaxation of the heart by exerting a suction force.

That the pericardium is not an essential structure is indicated by the fact that animals or people from whom it has been removed may continue to live normally.

The pericardial sac normally contains only a small amount of fluid. Pericardial effusions occur in various pathological conditions. In traumatic pericarditis in cattle the amount of fluid in the pericardium may be very great. It has been shown experimentally in small animals that when intrapericardial pressure exceeds venous pressure, the latter rises and ventricular filling is interfered with. The rise in venous pressure, however, tends to overcome the resistance to inflow caused by the increased intrapericardial pressure, so that the latter may rise considerably before a critical point is reached. At the critical level of pressure within the pericardium, ventricular output and arterial pressure decrease markedly.

Chapter V

THE PHYSIOLOGY OF THE HEART (CONTINUED)

THE CAUSE OF THE HEART BEAT

THE question of the cause of the heart beat is an old one toward the solution of which much speculation and experimentation have been directed. It cannot be said, however, that a complete understanding of the problem is even near, though a great deal of information has accumulated from time to time that points toward a solution.

The heart is not dependent for its beat upon its connection with the central nervous system. This fundamental conception has been held for years, and there is ample proof of its correctness. The simplest way to prove that the heart, unlike skeletal muscle, is able to continue its activity in the absence of connection with the central nervous system is to cut all nerves—vagus and sympathetic—leading to the heart. Under these conditions it continues to beat. The proof may be made more convincing by completely removing the heart from the body of the animal, whereupon, if it is kept under appropriate conditions, it will continue to beat for a long time. The frog's heart does not require the care upon excision that the mammalian heart does. The frog's heart is capable of beating for some time without any attention other than immersion in warm physiological saline or Ringer's solution. If it is actually perfused with warm Ringer's solution, it may continue beating for several days. The excised mammalian heart requires better conditions. A perfusion fluid must be made to pass through the coronary vessels. The temperature of the perfusate must be close to that of the body, and its oxygen tension and hydrostatic pressure must be adequate. An organ or tissue that continues to act in the absence of connection with the central nervous system is said to be *automatic*, or capable of developing its own stimulus to function. The heart, according to the results of experiments such as those just described, must be regarded as an automatic organ.

Myogenic and Neurogenic Theories of the Heart Beat. The heart is essentially a muscular organ, although there is a good deal of nervous tissue in its make-up. These nerve elements, consisting of cells and fibers, are especially abundant in the region of the S-A node, the A-V node, and the A-V bundle (Meiklejohn).

There are two principal theories relative to the origin of the stimulus for the heart beat. (1) The *myogenic theory* in its modern form holds that the excitatory impulse originates in the muscle cells of the S-A node and is then transmitted to the atria by way of the interatrial musculature and to the ventricles by way of the A-V node and its bundle. (2) The *neurogenic theory* holds that the impulse begins in the nerve tissue of the heart and is then transmitted to the muscle cells of the heart by way of the conducting system. While the majority of physiologists at the present time favor the myogenic theory, it is not possible to make a final statement as to which of the theories is correct. In support of the myogenic theory the following evidence may be cited:

1. The heart of the embryo chick begins to beat before nerve cells have made their appearance in it. The force of this observation is somewhat weakened by the argument that while the beat of the embryonic heart may be myogenic this is no proof that the adult heart beat is similarly originated; nerve cells may later assume the role of initiating the heart beat.

2. Atropine paralyzes a good share, perhaps all, of the nerve tissue found in the heart, yet the beat continues.

3. Strips of muscle apparently devoid of nerve tissue may be cut from certain regions of the ventricle. These isolated strips when perfused with a nutrient saline solution, or even when simply immersed in the solution, may contract rhythmically.

4. A widely accepted view of the significance of the nerve cells and fibers in the heart wall is that they are the effector neurons of the inhibitory apparatus of the heart. If this is true it is unlikely that they would also be concerned in initiating the heart beat.

The heart of the king crab (Limulus) stops beating when its nerve tissue, which is easily accessible, is removed (Carlson). It appears, therefore, that the heart beat of Limulus is neurogenic. One is not justified, however, in applying this conclusion to the heart of mammals.

For a general discussion of myogenesis versus neurogenesis, the book by Alvarez is suggested.

The Fundamental Stimulus. As just stated, the beat of the heart is probably myogenic in origin. This tentative conclusion does not, however, furnish any idea of the fundamental cause of the automatic rhythmic activity of the heart. The issue must be carried a step further and the fundamental stimulus of the heart sought. In approaching this subject it would perhaps be expected to find the stimulus connected in some way with the composition of the blood or lymph bathing the muscle cells. This view came into prominence with the discovery by Ringer, in 1874, that the excised frog's heart continues to beat for a long time if perfused with a solution of the chlorides of sodium, calcium, and potassium, in proper proportion. Such a mixture is known as Ringer's solution, the exact composition of which has been varied by different workers. A frequently used formula is as follows:

RINGER'S SOLUTION

Sodium chloride	0.7 per cent
Potassium chloride	0.03 per cent
Calcium chloride	0.026 per cent
Sodium bicarbonate	0.003 per cent

Later it was shown that the excised mammalian heart also may be kept beating for a considerable time if fed with a modified oxygenated Ringer's solution. Locke's solution, often used for the heart of mammals, has the following composition:

LOCKE'S SOLUTION

Sodium chloride	0.92 per cent
Potassium chloride	0.042 per cent
Calcium chloride	0.012 per cent
Sodium bicarbonate	0.015 per cent
Glucose	0.1 per cent

The results of numerous investigations on the hearts of frogs and mammals tend to show that sodium chloride exerts a part of its favorable effect by furnishing a necessary osmotic pressure to the fluid bathing the heart; that potassium and, in less degree, sodium exert a depressing effect on the beat of the heart, favoring diastole; and that calcium exerts a stimulating effect, promoting systole. Thus when calcium is absent from the perfusion fluid but sodium and potassium are present, the heart soon stops in diastole; whereas when calcium alone is present it soon comes to a standstill in a condition of extreme systole, known as calcium rigor. Both of the stoppages can be reversed by using a more normal perfusion fluid. It has been shown that sodium chloride can be replaced to a large extent by any nonelectrolyte that is nontoxic and does not enter the cells, for example, cane sugar; that potassium can be completely replaced by rubidium and imperfectly by cesium; and that calcium can be replaced almost completely by strontium but by no other cation (Clark, 1927).

However, it should not be concluded from the foregoing that the ions of sodium, potassium, and calcium are the ultimate stimulus of the heart; such a view would be unwarranted. It is evident, however, that the development of the stimulus is in some way dependent upon, or conditioned by, the presence of these ions. Work by Andrus and Carter suggests that the ions owe their effects to changes induced in the permeability of the limiting membrane of the muscle cell. These changes cause alterations in the rate of development and discharge of electrical potential across the semipermeable cell membrane. The potential difference is the result of a difference in the concentration of hydrogen ions within and without the cells. The greater concentration occurs within the cells because of the constant production of hydrogen ions there as a result of metabolism and because of the neutralizing influence of the buffers in the tissue fluids outside the cells. The pacemaking influence of the sino-atrial node is explained on the assumption that the condition of the cell membrane in this region is such that the potential is built up more rapidly, or the discharge takes place at a lower level, than in other parts of the heart.

Other facts and theories relating to the fundamental stimulus of the heart could be given, but no real answer to the question of its exact nature is available.

The Metabolism of Heart Muscle. Whatever the ultimate stimulus of the heart may be, the energy for cardiac contraction must come, of course, in the long run from the oxidation of organic substances brought to the heart by the blood. The oxygen consumption of the heart doing moderate work in the heart-lung preparation is of the order of 350 cc. per 100 gm. per hour (Evans). When the work of the heart is increased, or when the heart rate is increased without an increase in mechanical work, the oxygen consumption goes up. With a constant heart rate, there is a high positive correlation between diastolic volume and oxygen consumption.

An important question with respect to the metabolism of cardiac muscle is the nature of the foodstuff oxidized. Studies of the respiratory quotient (p. 445) of the heart show that it is usually high (0.8 to 0.9) but may fall to a low level during carbohydrate shortage. It may therefore be concluded that the heart can oxidize not only carbohydrate but other substances as well. Furthermore, studies of the carbohydrate utilization of the heart show that this is usually too small to account for all the oxygen consumption. The low respiratory quotients sometimes met with (0.7) tend to show that fat is the other substance oxidized. In addition, direct examination of the blood and heart in the heart-lung preparation suggests that the heart can use fat for energy purposes. The evidence fails to show that amino acids are oxidized for energy by the mammalian heart.

Experiments indicate that the heart is capable of utilizing large amounts of lactic acid, as much as 40 per cent of the total metabolism being due to the oxidation of this substance. Cardiac muscle contains significant amounts of glycogen, and it has been suggested that blood glucose is used mainly to restore glycogen, which is converted to lactic (or pyruvic) acid for oxidation.

RESPONSE OF HEART MUSCLE TO STIMULATION

Heart muscle when stimulated artificially responds differently in several respects from skeletal muscle, and some fundamental properties of heart muscles have been revealed in this way. The amphibian heart is suitable for such a study.

All Contractions Maximal. By this is meant that if heart muscle responds at all to stimulation, it contracts with the greatest strength possible for the particular condition of the muscle at the moment; it is also referred to as the all-or-none principle. This fact can easily be shown by tying a ligature around the frog's heart at the sino-atrial junction, whereupon the atria and ventricle, cut off from the sinus venosus, stop beating for a time. The tip of the quiescent ventricle may then be pierced with a bent pin, which is connected by a thread to a light lever. The lever is arranged to write on a kymograph, and provision is made for electrical stimulation. Excitation of the ventricle, if the stimulus is above the threshold, causes as extensive a contraction with a weak stimulus as with a strong one. Mammalian heart muscle has been shown to respond similarly. In this respect heart muscle differs markedly from skeletal muscle, the extent of the contraction of the latter being dependent upon the strength of the stimulus applied. The explanation of the difference in the response of these two classes of muscle is believed to lie in their histological structure and not in any fundamental physiological differences. Cardiac muscle fibers form a syncytium, that is, freely anastomose, so that a stimulus applied to any part of the ventricle passes to all other parts, thus throwing the whole heart into contraction. On the contrary, skeletal muscle fibers are separated from one another by a distinct sarcolemma, which prevents spread of the stimulus from fiber to fiber. In skeletal muscle, therefore, only those fibers that are directly stimulated contract, and different degrees of contraction are brought about by stimulating different numbers of fibers. It thus appears that all-or-none response is not a special property of cardiac muscle but is exhibited also by the individual fibers of skeletal muscle.

Staircase Effect. If the ventricle, made quiescent as indicated above, is stimulated with single effective shocks at intervals of, say, two to five seconds, and the height of each contraction is recorded on a kymograph, it will usually be found that the first four or five contractions form an ascending series. This is known as the staircase effect, or treppe. It is not a contradiction of the all-or-none law, for the strength of stimulation remained the same. It means that some improvement in the condition of the cardiac muscle has taken place as a result of the first few responses to stimulation. The nature of the favorable change which occurs is unknown.

The Refractory Period of the Beat. When stimulated during systole, heart muscle can show no additional contraction, for, according to the all-or-none principle, it is already contracting maximally. The period of systole is therefore an absolutely refractory period. The end of the T wave of the electrocardiogram marks approximately the end of the absolutely refractory period. Following this period there is a relatively refractory period during with the excitability of the heart is increasing but has not yet returned to normal. The relatively refractory period occurs early in diastole.

The refractory period can be illustrated on the exposed, beating heart of the frog connected with a muscle lever as above described. If the stimulus is applied to the ventricle during systole, no change in the tracing occurs; the heart is refractory. When, however, the stimulus is applied during diastole, a premature systole followed by a compensatory pause occurs, and the pause is the longer the earlier in diastole the stimulus is applied. During the relatively refractory period a stronger stimulus is required to evoke a response than during the rest of diastole. The explanation of the compensatory pause is simple: it occurs because the next regular rhythmic discharge from the sinus venosus to the ventricle, instead of evoking a normal ventricular systole, falls in the refractory period of the premature contraction and is therefore ineffective. The ventricle must then await the next discharge from the sinus venosus before it can contract. Because heart muscle possesses a long refractory period it cannot be tetanized, that is, thrown into continuous contraction by a rapid series of stimuli, as can skeletal muscle.

The phenomena of refractory period, premature beat, and compensatory pause apply also to mammalian heart. Electrical or mechanical stimuli to the heart may be used.

THE NERVOUS REGULATION OF THE HEART

It has already been stated that the heart is an automatic organ, that is, that it generates its own stimulus for contraction and is therefore not dependent upon the nervous system for the cause of its beat. In spite of the fundamental automaticity of the heart, it is constantly influenced by the nervous system, which regulates the frequency and force of the beat. The function of the cardiac nervous mechanism is to insure the proper co-ordination and adjustment between the beat of the heart and the blood requirements of different parts of the body. In the absence of this regulatory influence, the heart inadequately meets the demands placed upon it.

The Efferent Cardiac Nerves. The efferent nerves by which the heart is regulated are derived from the vagus and the sympathetic nervous system (Chapter XXXV). Most of the vagal cardiac fibers tend to slow or stop the heart beat. They are therefore referred to as the cardio-inhibitory nerve fibers. The sympathetic cardiac nerves tend to accelerate the beat and to increase its force and are therefore termed the accelerator nerves. Recent work has shown the presence of accelerator fibers in the vagus nerve, especially the right.

An extensive anatomical study of the innervation of the heart of the dog and cat has been made by Nonidez.

The Cardio-inhibitory Nerves. The cardio-inhibitory fibers, contained in the vagi, leave these nerves and pass to the heart by way of the cardiac plexus. The cardio-inhibitory fibers belong to the parasympathetic division of the autonomic nervous system. They therefore have peripherally located nerve cells around which the preganglionic fibers terminate and from which postganglionic fibers arise to pass to their destination. The cells of origin of the postganglionic fibers are believed to be the numerous nerve cells found within the heart itself.

The action of the inhibitory fibers is to slow the heart or even stop it for a short time in diastole, as may be shown by isolating the vagus nerve in the neck of an animal, dividing it, and stimulating its peripheral end. The tendency of the right vagus nerve when stimulated to cause complete inhibition is greater than the tendency of the left. The blood pressure is usually greatly reduced by the stimulation. Some effects of vagus stimulation are shown graphically in Figs. 32 and 33. The inhibitory action of the vagus is true not only of mammals but of animals far below the mammals. In mammals the action at birth is often weak or absent (Kellogg, Huggett); in such cases inhibition is increased or acquired later.

The question of the place of action of the vagus fibers on the heart has frequently arisen. The action is principally on the atria. The right vagus affects mainly the sino-atrial node, whereas the left often affects the A-V node and bundle. There is little or no direct action of the vagi on the musculature of the mammalian ventricle. However, on the frog ventricle depression is powerful (Clark, 1927). If vagus stimulation has caused complete inhibition of the heart, the ventricles, but usually not the atria, escape from the inhibition and begin to beat again even though the stimulation is maintained. Ventricular escape results from the development of an ectopic rhythmic center in a ventricular portion of the conducting system of the heart.

The cardio-inhibitory nerve fibers are in a state of tonus. This means that they are constantly discharging inhibitory impulses to the heart. It will be shown later that the tonus of these fibers is dependent upon the tonus of their cells of origin in the medulla oblongata. That these nerve fibers are in a state of tonus is easily proved by cutting the vagus nerves, whereupon the heart rate is increased (Fig. 34). The normal intensity of inhibitory tonus, and the consequent increase in heart rate following section of the vagi, vary in different

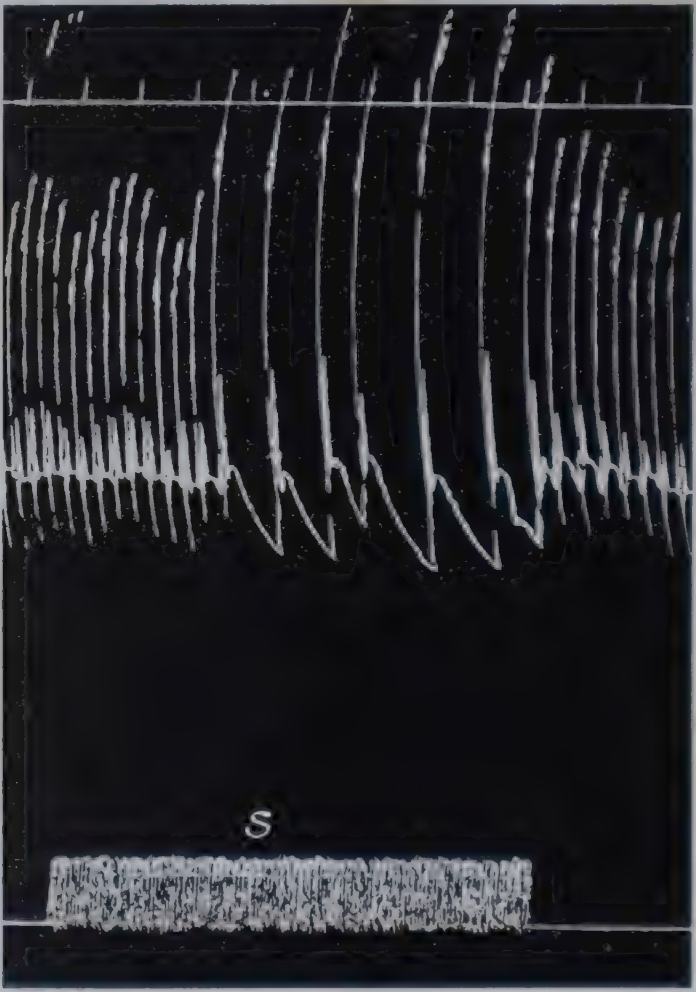

FIG. 32.—Showing slowing of the heart due to stimulation of the peripheral end of a cervical vagus nerve (pig). The signal (s) indicates the duration of the stimulus. The slowing of the heart was accompanied by larger beats. During the longer diastoles the ventricles were filled more completely and, in accordance with the law of the heart, gave more forceful beats.

animals. Animals with small hearts in relation to body weight (nonathletic animals) have relatively rapid pulses when at rest, and section of the vagi can cause little acceleration; whereas animals with large hearts in relation to body weight (athletic animals) have relatively slow pulses when at rest, and section of the vagi causes great acceleration. A rabbit, an animal with a small heart, had a normal pulse rate of 205 and a pulse rate after vagal section of 321, an increase of only 56 per cent; whereas a hare, an animal with a large heart, had a normal pulse rate of 64 and a pulse rate after vagal section of 264, an increase of 312 per cent (Clark, 1927). The heart of the pig shows only a relatively small percentage increase after vagus transection or the injection of atropine, which paralyzes vagus endings in the heart (Dukes and Schwarte).

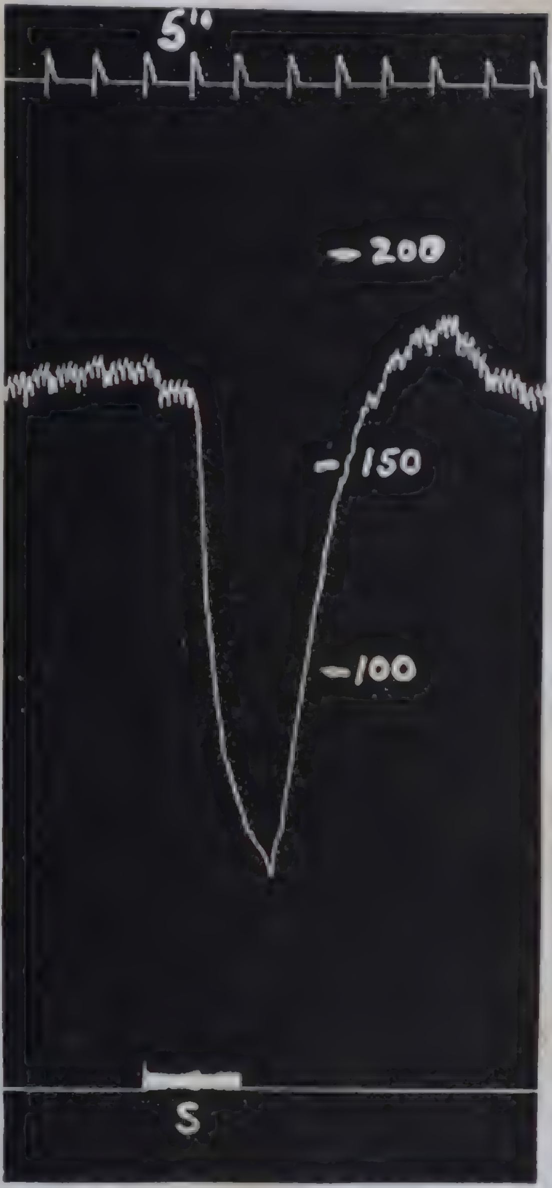

FIG. 33.—Effect of stimulation of the peripheral end of a vagus nerve (left) on the heart beat and blood pressure (horse). The signal (s) indicates the duration of the stimulus. A mercury manometer was connected to the central end of a carotid artery. A clamp on the rubber tube leading from the arterial cannula to the manometer was partly closed in order to damp the oscillations of the mercury. Chloroform anesthesia.

It is now generally held, on the basis of very substantial evidence, that the vagi exert their inhibitory effect by liberating in the heart the chemical substance acetylcholine. In fact, the evidence strongly indicates that most, probably all, parasympathetic nerve fibers exert their effects by liberating acetylcholine at their terminations. Such fibers are said to be cholinergic.

The Accelerator Nerves. Most of the accelerator nerves of the heart are derived from the sympathetic system. The preganglionic fibers leave the spinal cord on each side in the ventral roots of the second, third, fourth, and fifth thoracic nerves. The synaptic junctions of the preganglionic fibers are situated in the first thoracic and the last cervical ganglia. From cells in these ganglia the accelerator nerves arise, as postganglionic fibers, and run to the heart in the cardiac plexus in close relation to the inhibitory nerves.

Evidence obtained in recent years (Kabat; Brouha and coworkers) indicates that some of the accelerator fibers of the heart run in the vagi, especially the right vagus. These fibers originate from nerve cells in the medulla and are not distributed through the sympathetic system. They are believed to be capable of reflex excitation in the normal animal, for experiments indicate that they play a part in the reflex acceleration of the heart which occurs when there is a fall of blood pressure (Haney, Lindgren, and Youmans).

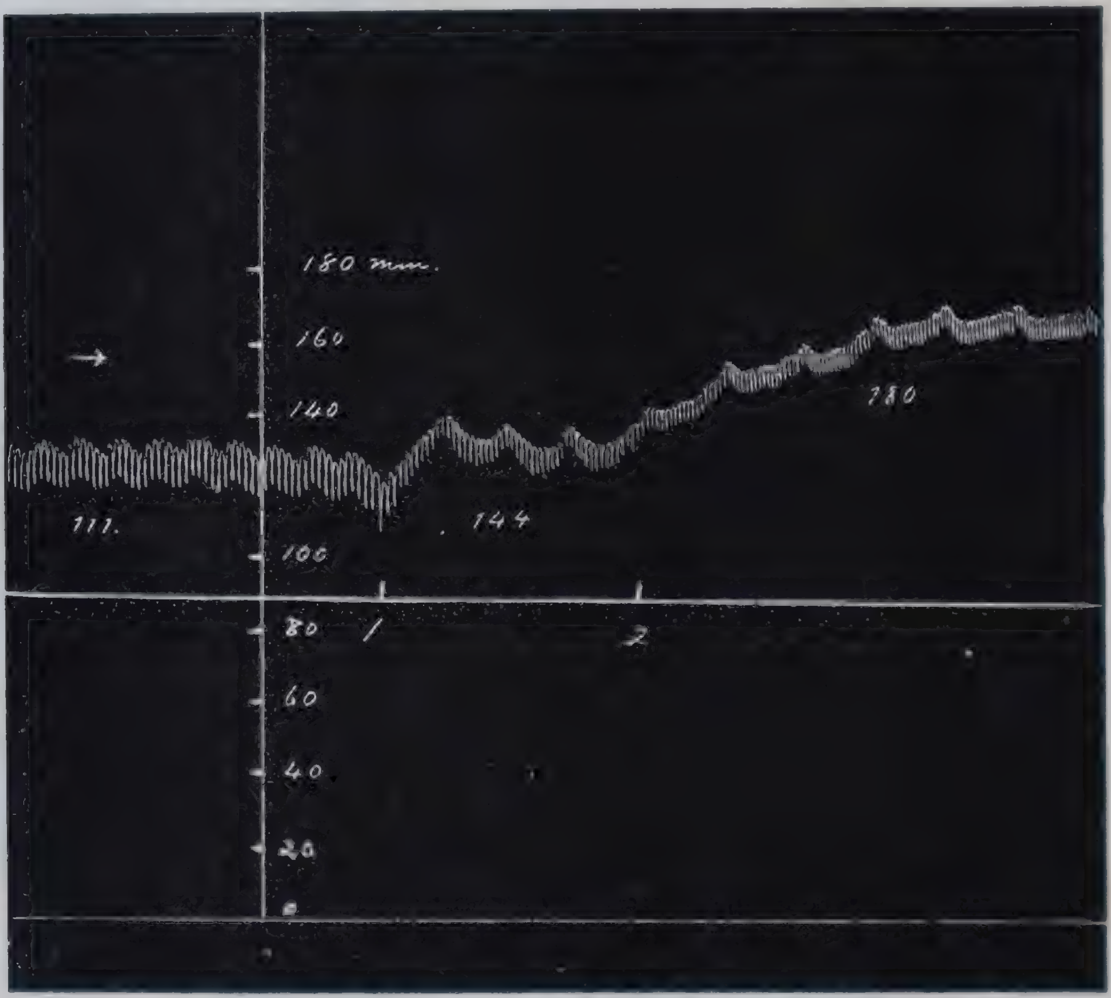

Fig. 34.—Effect of section of the vagi on the heart rate and blood pressure (dog). At *1*, the right vagus was sectioned; at *2*, the left vagus. The numerals along the blood pressure curve indicate the heart rate. (Dawson; from Howell's *Physiology*; copyright—W. B. Saunders Company.)

The action of the accelerator nerves on the heart is opposite to that of the inhibitory nerves. Stimulation of the accelerator nerves usually causes the heart to beat faster (Fig. 35). Excitation of the accelerator nerves may cause an increase in the force of the beat. This may be reflected in beats of larger size (Fig. 36). The increases in rate and force may occur simultaneously or separately. If a great increase in rate occurs, the stroke volume may decrease. The increase in rate which accompanies stimulation of the accelerator nerves is brought about by an action on the S-A node, whereas the increase in force is brought about by direct action of the accelerator nerves on the musculature of atria and ventricles. The sympathetic nerves, therefore, unlike the vagi, influence the ventricles. This is apparently true in all vertebrates. Sometimes during sympathetic stimulation the pacemaker of the heart shifts to the A-V node, the irritability of which

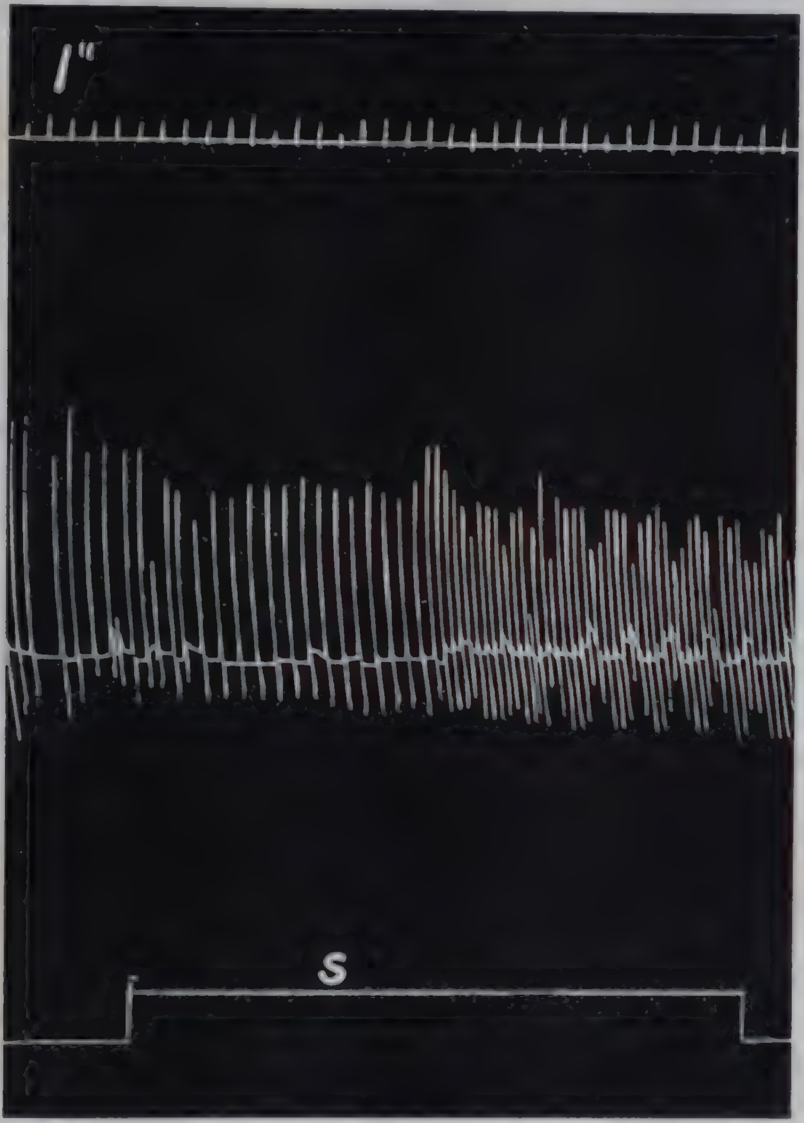

FIG. 35.—Showing acceleration of the heart (pig) due to stimulation of an accelerator nerve (filament of left cardiac plexus). The signal (s) indicates the duration of the stimulus. There was a lag of about 13 seconds between the beginning of the stimulus and the beginning of the acceleration. The return of the heart rate to normal is not shown.

has been increased by the stimulation. The shift may be revealed by electrocardiographic studies.

The accelerator nerves are in a state of tonus. This is indicated by experiments of Bronk and co-workers, who recorded the electrical changes (action potentials) in the accelerator nerves arising from the stellate ganglia. A continuous discharge of impulses exerting a tonic accelerator and augmentor effect on the heart was noted. The frequency of the impulses was usually less than 10 or 15 per second. The discharge in the accelerator nerves was influenced by reflexes and by changes in the chemical composition of the blood.

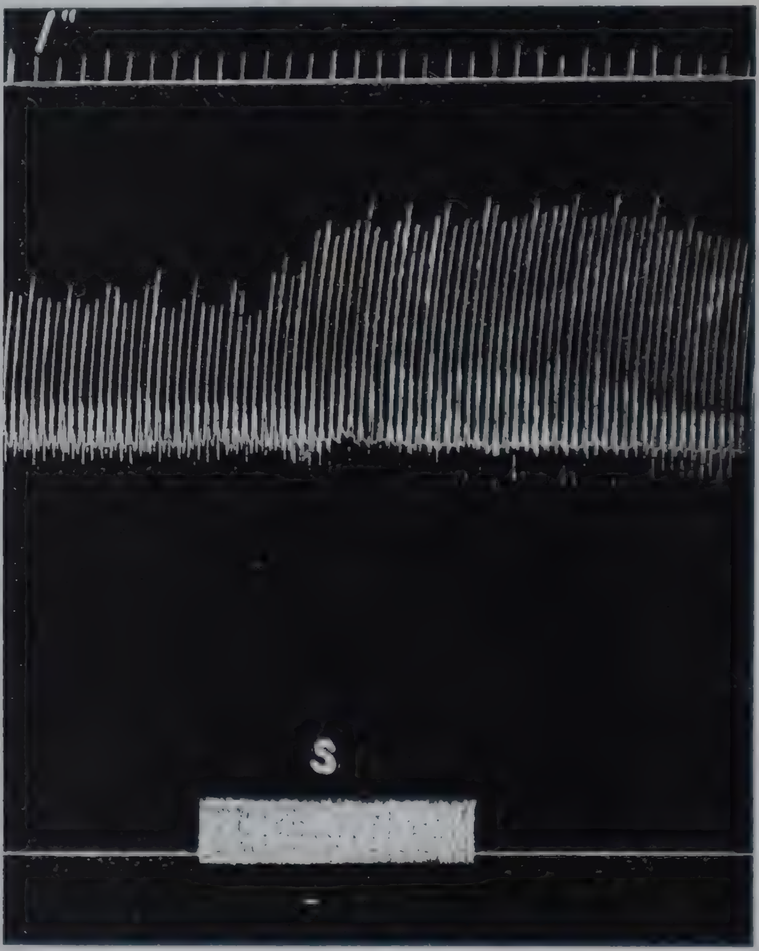

Fig. 36.—Showing augmentation of the heart beat due to stimulation of a branch of the cardiac plexus (pig). The signal (s) indicates the duration of the stimulus. Note the absence of cardiac acceleration.

Recent work indicates that the accelerator nerves exert their effect through the liberation in the heart muscle of a substance closely allied to or identical with the hormone adrenaline. In fact, evidence is strong that this substance—sympathin—mediates the action of most sympathetic nerve effects in the body. Nerve fibers producing sympathin at their terminations are said to be adrenergic.

Cardiac Reflexes. The tonus of the cardio-inhibitory and cardio-accelerator fibers is dependent upon the tonus of the cardiac reflex centers in the medulla oblongata. The cardio-inhibitory center, from which the cardio-inhibitory fibers arise, is located in the dorsal nucleus of the vagus. The accelerator center, from which the accelerator paths originate, is probably also located in the medulla oblongata, although its position has not been determined. In close physiological and anatomical relationship with the cardiac centers are the vasomotor centers, by which the caliber of the blood vessels is regulated. Vasomotor control is discussed in another chapter.

Each of the cardiac reflex centers is influenced by the inflow of afferent nerves impulses from several sources, and it is by reason of this continual bombardment that the tonus of the centers is maintained and varied. The tonic activity of either center may be reflexly increased or decreased. Because of this the heart is under a very flexible nervous regulation. It is usually believed that most of the regulation takes place through the inhibitory mechanism. Experiments by Murphy on dogs suggest, on the other hand, that the function of the inhibitory mechanism is to maintain a basal heart rate slower than that seen under ordinary circumstances. Under usual conditions a faster heart rate obtains because of reflex reduction of the tone of the cardio-inhibitory center and reflex stimulation of the accelerator center. When the animal is kept in quiet surroundings and is thus shielded from its environment, the heart rate, under the influence of the inhibitory mechanism, slows to its basal level, and no activity of the accelerator mechanism is evident. The accelerator mechanism is therefore regarded as an emergency mechanism helping to maintain the faster heart rate, together with its variations, which characterize ordinary existence.

The statement that the cardiac reflex centers are influenced by afferent impulses from several sources needs amplification. Stimulation of the central end of practically any nerve containing afferent fibers may cause reflex alteration of the heart rate. But the most important reflex effects on the heart are brought about by stimulation of nerves whose receptors are situated in the aortic arch, in the carotid sinus, and in the heart itself.

Located in the wall (adventitia and media) of the *aortic arch* are nerve endings the stimulation of which causes reflex slowing of the heart and a fall of blood pressure. Under normal conditions these receptors are excited mechanically by the rise of blood pressure in the aorta at every beat of the heart. They are therefore pressure receptors. The nerve fibers transmitting these impulses constitute the aortic or depressor nerve. In most animals the aortic nerve runs to the medulla as a part of the vagus. In the opossum it is said to form an anatomically separate nerve. In the rabbit the fibers under consideration run in a nerve separate from the vagus, but the nerve is not made up exclusively of depressor fibers. It contains some pressor and efferent fibers as well (O'Leary, Heinbecker, and Bishop).

If the blood pressure rises, the aortic pressure receptors are stimulated, whereupon a reflex slowing of the heart and a fall of blood pressure take place. If the blood pressure falls below normal, there is a cessation of impulses via the aortic nerve. This releases the cardio-inhibitory center from the stimulating effect of the aortic nerve and the cardio-accelerator and vasoconstrictor centers from the inhibiting effect. The heart therefore beats faster and vasoconstriction take place. A return of blood pressure to normal occurs. So far as is known, there are no receptors in the aortic arch that are stimulated by the *fall* in pressure. The drop in pressure *releases* receptors from stimulation.

The slowing of the heart that results when the aortic nerve is stimulated doubtless takes place through both the cardio-inhibitory and the cardio-accelerator centers, the one being stimulated, the other inhibited. The vasodilatation is caused principally by an effect on the vasoconstrictor center, which is inhibited; but under conditions of strong stimulation of the aortic nerve the vasodilator center is also brought into action. The vasomotor responses are further discussed on p. 183.

Arising in the *carotid sinus*, a bulbous enlargement at the bifurcation of the carotid artery, is an afferent nerve—the sinus nerve, a branch of the glossopharyngeal—stimulation of which likewise causes reflex cardiac inhibition and a fall of blood pressure. This nerve has pressure receptors in the wall of the carotid sinus which are excited at every beat of the heart by the rise of blood pressure in the sinus. The carotid sinus mechanism works on exactly the same principle as the aortic depressor mechanism just described. Stimulation of pressure receptors in the carotid sinus by an intrasinusal rise in pressure causes nerve impulses to pass to the centers in the medulla concerned in the reflex regulation of the circulation. The cardio-inhibitory center is stimulated and the cardio-accelerator center is depressed (Fig. 37). Thus the heart rate is decreased. The vasoconstrictor center is inhibited and under some conditions the vasodilator center is stimulated. Thus the blood pressure falls.

The aortic and sinus nerves are sometimes referred to as the moderator or buffer nerves. By causing cardiac slowing and vasodilatation they prevent the blood pressure from rising too much. They are therefore of great concern in the normal regulation of the circulation. In the regulation of the heart rate the afferent mechanism of the aorta is more important than that of the carotid sinus (Winder).

According to the work of Bainbridge and of others the rate of the heart is kept reflexly adjusted to the rate of venous flow into the right atrium. When the venous inflow is augmented, nerve impulses pass to the medulla oblongata by way of the vagi. These impulses decrease cardio-inhibitory tone and to some extent increase accelerator tone, and so cause an increase in heart rate. This reflex is often termed the Bainbridge reflex. The location of the receptors for the Bainbridge reflex is usually stated to be the region at the *root of the anterior vena cava*. Recent work by Ballin and Katz confirms the existence of the Bainbridge reflex in most of the dogs studied, but these authors were unable to obtain definite evidence as to the location of the receptors. Some of the observations suggested that reflexes originating in the pulmonary vessels and heart chambers other than the right atrium might be involved.

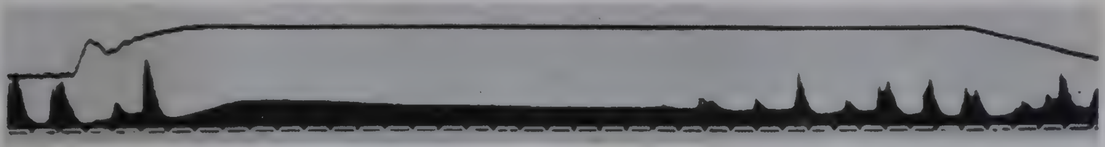

FIG. 37.—Inhibition of sympathetic impulses to the heart by raising the pressure in the carotid sinus. The upper record shows the pressure variations in the sinus; the lower record, action potentials in sympathetic fibers to the heart. (From Bronk, *Research Publications of the Association for Research in Nervous and Mental Disease,* 1940, 20.)

The *aortic* and *carotid bodies* contain nerve endings (chemoreceptors, chemoceptors) which respond to certain chemical changes in their environment. These chemoceptors are concerned in the reflex regulation of the circulation. They are discussed elsewhere (p. 187).

The *hypothalamus* can influence the activity of the heart via the cardiac nerves. However this part of the brain-stem is not essential to cardiac control (p. 185).

The *cerebral cortex* is capable of affecting the cardiac centers in the medulla. The changes in heart rate that accompany such psychic states as anger, fear, and embarrassment suggest that this is so. Experimentally it has been shown that electrical stimulation of any one of a large number of regions of the cerebral cortex can bring about cardiovascular changes, including cardiac acceleration (p. 186).

The principal drive of the cardiac nerve centers is derived reflexly. Yet it is probable that under some conditions *chemical stimuli* in the blood bathing the centers are of importance in determining their action. An increase of carbon dioxide or a decrease of pH may stimulate the cardio-inhibitory center. It is doubtful, however, if under ordinary conditions these factors are of much significance in the regulation of the centers.

Some Cardiac Nervous Effects in the Pig and Sheep. Very little work has been done on cardiac regulation in farm animals. Dukes and Schwarte made some observations on this topic and on vasomotor responses (p. 190) in the pig. The evidence indicated that vagus tone was fairly well developed. Cardio-inhibitory power was better developed in the right vagus nerve than in the left. Stimulation of the cardiac plexus of the pig gave acceleration and augmentation of the heart beat.

Rangsit studied certain cardiac nervous and vasomotor (p. 190) reactions in sheep. The degree of vagus tone as indicated by the increase in heart rate following injection of atropine varied. In some animals it was very definite, whereas in others it was slight. Stimulation of the peripheral end of one vagus nerve never caused complete inhibition of the heart. Complete inhibition upon stimulation of the peripheral ends of both vagi was not the usual response.

CHEMICAL REGULATION OF THE HEART

That the heart is subject to nervous control has just been considered. That chemical factors are also concerned in cardiac regulation is generally recognized. But it is a question whether a specific chemical regulator—a heart hormone—is involved in cardiac control. Most investigators have been unable to confirm the idea of a heart hormone.

Among the chemical factors affecting the heart beat the following may be mentioned: (1) certain cations, Na, Ca, K, present in the blood and tissue fluids (p. 115), (2) adrenaline, and (3) carbon dioxide and other acid products of metabolism.

The effect of adrenaline on the heart may be studied on an isolated preparation perfused with Locke's solution. The hormone is added to the perfusate. Both the rate and the amplitude of the beat are increased (Fig. 38). This is brought about by stimulation of the sympathetic terminal mechanisms in the heart. The oxygen consumption of the heart is increased. In the intact animal adrenaline injection usually causes some degree of reflex slowing of the heart because of the stimulation of the aortic and carotid sinus receptors by the high blood pressure, which results from widespread vasoconstriction.

Carbon dioxide is a waste product of cellular metabolism. However, it is more than this. It exercises favorable, in some cases indispensable, controlling effects in the body. Within limits carbon dioxide exerts a stimulating effect upon the heart, increasing both the force and the frequency of the beat. Other acid products of metabolism probably act similarly.

THE EFFECT OF TEMPERATURE ON THE HEART

The frequency of any rhythmically acting tissue varies, within limits, almost linearly with the temperature to which it is subjected. The response of the heart to changes in the temperature of the fluid bathing its cells may be studied by perfusing the isolated organ with a nutrient fluid whose temperature can be varied. Under these conditions it is found, in both cold-blooded and warm-blooded hearts, that the changes in temperature and frequency, within limits, practically parallel each other (Knowlton and Starling). The low temperature limit for mammalian heart action is about 17 degrees C., while the upper limit is about 45 degrees C. The low limit for efficient action appears to be about 23 degrees.

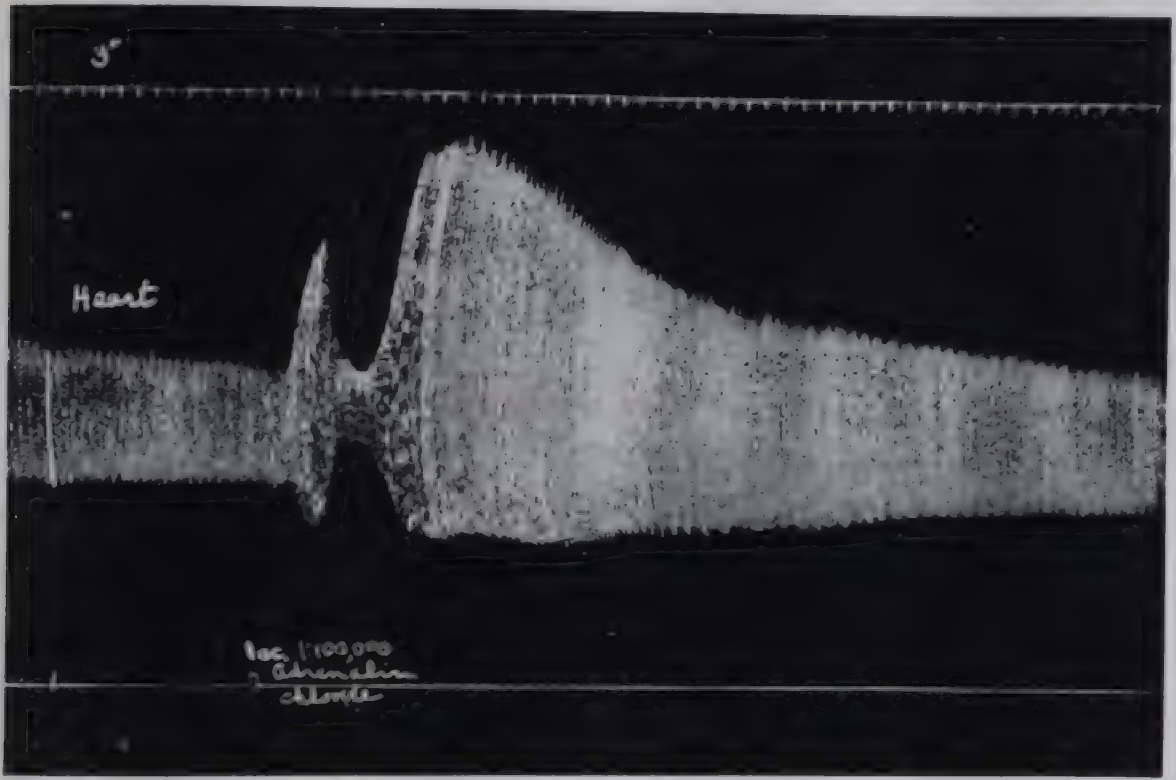

Fig. 38.—The effect of adrenaline on the isolated heart (rabbit). At the signal the hormone was injected into the perfusion fluid feeding the heart. Both the rate and the amplitude of the beat are increased. (From Dukes and Batt, *Cornell Veterinarian*, 1941, 31.)

Landsteiner and Hayes investigated the effect of the temperature of the blood on the heart rate by injecting physiological salt solution at various temperatures into the jugular vein of intact anesthetized cats and rabbits. Infusion of cool solutions (22 degrees C. to 36 degrees C.) caused a slowing of the heart of 20 to 100 beats below the normal. Infusion of saline solutions at body temperature caused no change in the heart rate. Infusion of warm saline solution (43 degrees

C. to 57 degrees C.) caused acceleration of the heart of 10 to 90 beats above the normal. The effect of the infusions on the heart rate was not altered by bilateral vagotomy nor by the type of anesthetic used. In general the lower the temperature of the saline solution injected the more pronounced was the bradycardia; the higher the temperature the more pronounced the tachycardia.

The heart acceleration that accompanies fever is largely due to the direct action of the increased temperature on the heart itself. Thus the metabolic rate of the heart is increased.

HEART RATE

As a rule smaller animals have a faster heart rate (pulse rate) than larger animals. This is related to the fact that the smaller animals have a higher metabolic rate per unit of body weight. It is pointed out by Brody that the pulse rate is directly proportional to the basal oxygen consumption per unit of body weight in mature animals of different species.

The inverse relationship between heart rate and body size applies both within the species and among the different species. For example, a small dog may have a heart rate of 120 beats per minute, whereas a large dog may show a rate of only 80 or less. The heart rate of the mouse is some 600 beats per minute; rat, 400; guinea pig, 280; elephant 30.

In some species there is a sex difference in the heart rate, but this is not present in all species.

Young animals have a faster heart rate than mature animals. This is illustrated in the horse and ox by the accompanying data (p. 132) from Ellinger as cited by Tigerstedt. The faster rate in young animals is explained in part by their smaller size. Another factor is that tonic vagal inhibition is less developed in young animals.

A seasonal variation in heart rates of dairy cows has been reported by Ralston and co-workers. The fastest rates were seen in April and October, the slowest in June and August.

Other physiological factors influencing the heart rate are excitement, muscular exercise, high environmental temperature, digestion, and sleep. Changes in heart rate are seen in a variety of pathological conditions.

Resting heart rates of animals are shown in the table on the following page.

As a part of their electrocardiographic studies on normal dairy cattle, Alfredson and Sykes determined the heart rates of the animals. The mean rate for all the cattle was 71.6 beats per minute. The standard error of the mean was 1.22 beats per minute. For animals up to

Heart Rate	
Horse	32-44
Horse (Thoroughbred)	38-45
Dairy cow	60-70
Sheep and goat	70-80
Pig	60-80
Dog	70-120
Cat	110-130
Chicken	200-400
Man	60-90

1½ years of age, the rate was considerably greater, the average being 82.5. For animals over 1½ years old, the average rate was 67.8.

Variations in heart rates of dairy cows have been studied by Blaxter. He points out that when counting heart beats with a stethoscope an initial high rate should be disregarded. Standing was found to increase the heart rate 5 to 7 beats per minute over lying. Rumination caused a slight increase in rate. Eating caused a definite increase in heart rate; at the end of a large meal rates of over 100 beats per minute were not abnormal.

The basal heart rate of the dog appears to be much lower than the rate when taken under ordinary conditions. Murphy determined the heart rates of normal quiet dogs that had been required to fast for 12 hours and had rested for an hour in a quiet room. The rates obtained under these conditions ranged from 50 to 56 beats per minute and were considered to be near basal. In the same group of dogs before special treatment the rates ranged from 80 to 130.

Basal heart rates below 40 have been reported in athletes (White).

Recent studies of the heart rate of the domestic fowl have been made by McNally and by Henderson and Hathaway. McNally's paper contains a summary of previously recorded rates.

THE EFFECT OF MUSCULAR EXERCISE ON THE HEART RATE

Increased muscular effort calls for more oxygen, which is largely supplied by increasing the minute output of the heart. As has been shown, this may be brought about by an increase in the stroke volume or the heart rate or both. That the heart rate is usually distinctly increased as a result of exercise is a familiar fact. The possible increase is directly correlated with the intensity of vagal tone at body rest. The increase in heart rate that accompanies exercise is caused by a number of factors, some of which are the following: (1) During exercise the motor discharges originating in the higher brain centers and passing to the skeletal muscles apparently affect the respiratory and cardio-inhibitory centers, stimulating the former and inhibiting the latter. This may help to increase the respiratory and cardiac rates at the very beginning and throughout the course of the exercise. Stimulation of the accelerator mechanism may also occur. (2) The increased venous return to the heart, caused by the augmented aspiratory action of the thorax and the massaging action of contracting skeletal muscles on the veins, may bring about acceleration of the heart by evoking the Bainbridge reflex. (3) With prolonged exercise a rise of temperature may be of importance in causing cardiac acceleration. (4) Liberation of adrenaline may be a factor.

CHANGES IN PULSE RATE WITH AGE

	Age	Pulse Rate
Horse................	8–10 weeks	60– 79
	6 months	60– 71
	10–12 months	50– 68
	2 years	44– 65
	3 years	39– 62
	4 years	36– 59
	5 years	36– 57
Ox..	Fetus	154–175
	Newborn	118–148
	6–12 hours	115–136
	2– 4 days	110–125
	8–14 days	105–115
	1 month	100–115
	3 months	90–105
	6 months	85–103
	1 year	80– 98

SOME CARDIAC IRREGULARITIES

Experimental Neurosis. Sheep in which this condition has been developed show a cardiac disorder characterized by a rapid and irregular pulse and by great sensitivity of the heart to stimuli which in other sheep produce no change in the heart action (Anderson, Parmenter, and Liddell).

Sinus Arrhythmia. This type of cardiac irregularity is very common in normal, quiet dogs and may be seen in other animals. It is due to alternate increase and decrease of vagal activity and usually bears a relation to the breathing, although this is not always true. The irregularity may be so pronounced as to be readily detected by auscultation of the heart or palpation of the pulse. The electrocardiogram reveals the presence of the usual waves in normal sequence. It is the spacing of the waves that is affected, the principal change being in the interval from T to P. This interval varies inversely with the heart rate.

Sinus arrhythmia in a normal dog is shown in Fig. 39.

Anything that diminishes the inhibitory control of the heart or increases the accelerator control will cause the arrhythmia to disappear. Thus excitement, exercise, anesthesia, and the administration of atropine are effective in abolishing the arrhythmia.

Heart-Block. In this condition there is defective transmission of impulses in the conducting system of the heart. Three stages of atrioventricular heart-block are recognized: incomplete, partial, and complete. In *incomplete heart-block* there is a prolongation of the atrioventricular conduction time (P-R interval of the electrocardiogram). In *partial heart-block* some of the impulses from the sino-atrial node fail to get through to the ventricles, which are not excited. The electrocardiogram reveals normal P waves but occasionally absent ventricular complexes (Q-T). In *complete heart-block* all impulses fail to reach the ventricles and the upper and lower chambers beat at independent rates, the ventricular rate being much slower than the atrial.

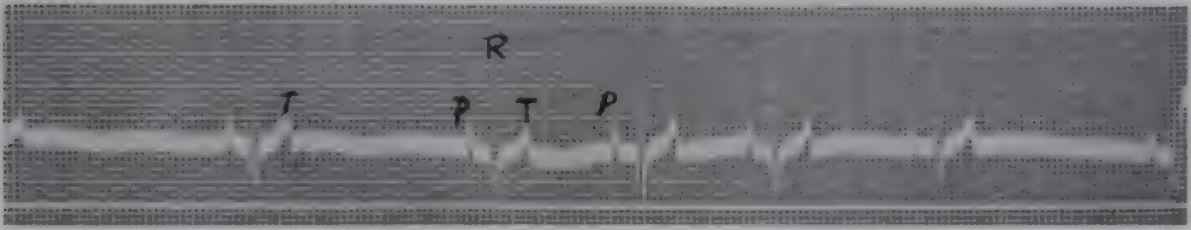

FIG. 39.—Sinus arrhythmia in a normal dog. Note the variations in the T-P intervals.

The various stages of atrioventricular heart-block can be produced by experimental compression of the A-V bundle or they may occur in clinical cases. All three stages of heart-block may be seen in horses (Dukes, Batt, Luisada, Roos). Partial heart-block of horses often disappears during excitement or after the injection of atropine. This suggests that such blocks are due to overaction of the vagus on the A-V node. An electrocardiogram of partial heart-block in a horse is shown in Fig. 40 and one of almost complete heart-block in Fig. 41.

Bundle-Branch Block. Experimental or clinical damage to a branch of the A-V bundle will produce, among other things, a characteristic prolongation and change in the form of the QRS group. Alfredson and Sykes (1940) observed in calves, however, that changes in the duration and form of the QRS after section of either bundle-branch were much less marked than in dogs. They suggest that differences in the intraventricular conducting system in the two species might explain the differences seen in the electrocardiograms of bundle-branch block. These same investigators have shown that the QRS group is prolonged and its contour and voltage changed in calves on a low-potassium diet.

Premature Beats. Heart muscle is refractory to stimuli applied during systole. However, atria or ventricles will respond with a premature beat if a stimulus is applied during the nonrefractory period. If the atria respond with a premature beat, the ventricles will also contract in due course. The premature contraction is followed by a compensatory pause (p. 118).

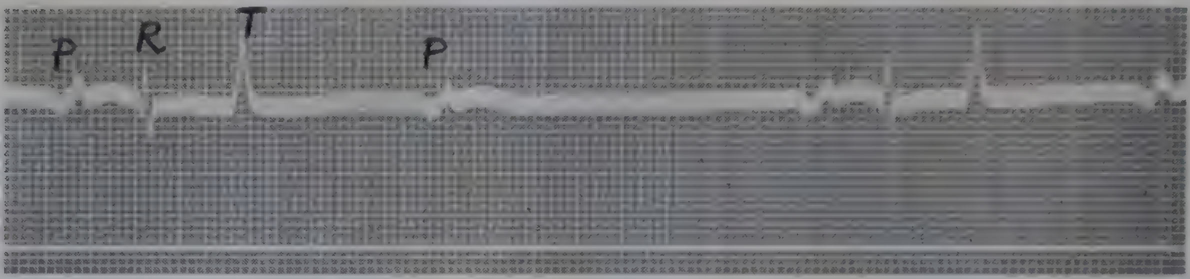

Fig. 40.—Electrocardiogram (lead III) of a horse showing partial heart-block. Note the absence of a ventricular complex after the second P wave. The diphasic P wave is not abnormal. The P-R interval (0.40 sec.) is longer than the average for horses. The wave after P is probably the so-called atrial T wave. which may be evident when the P-R interval is prolonged. The T wave shows a high voltage.

Any part of the myocardium or its conducting system may become the seat of the heightened irritability which causes a stimulus for a premature beat to arise.

Clinically occurring premature beats may be related to an interference with the blood supply to some part of the myocardium. The irritability of the ischemic region may thus be heightened to a point that it becomes a pacemaker setting off one or more premature beats.

Premature ventricular beats may occur under conditions of overaction of the vagi, particularly if there is an accompanying stimulation of the sympathetic nervous mechanism to the heart. The vagi supply the S-A node, the atria, and the A-V node but not the ventricular musculature. During vagus stimulation the normal pacemaker is inhibited but there is little or no direct effect on the ventricles. The sympathetic nerve supply reaches the ventricles. During inhibition of the normal pacemaker the sympathetic mechanism, particularly if its action is enhanced by emotional stress or by adrenaline, may cause the development of a ventricular ectopic center which will lead to premature beats or even to ventricular tachycardia.

Premature beats are not thought to be of common clinical occurrence in animals. However, no detailed study of the question appears to have been made.

Ventricular Fibrillation. When a coronary artery, or even one of its large branches, is occluded, the normal ventricular contractions soon cease and a condition known as ventricular fibrillation sets in. This incoordinate type of contraction, when fully developed, is quite ineffective in pumping blood. The blood pressure therefore falls to a very low level and death rapidly follows. Other causes of ventricular fibrillation are stimulation of the ventricle with induction shocks or with condenser discharges of fairly high frequency (10 to 15 shocks per second or higher); stimulation with an alternating current of relatively low voltage or with direct current; thermal, mechanical, or chemical irritants applied to the heart; and toxic doses of chloroform, digitalis, and other drugs.

Single induction shocks or single condenser discharges seldom cause fibrillation, but single shocks with direct (galvanic) current may precipitate this condition.

Intravenous injections of calcium salts for therapeutic purposes in cows may result in acute toxicity and, occasionally, in sudden death. The chloride is more dangerous in this respect than the gluconate. Ventricular fibrillation is probably the usual cause of death when it occurs under these circumstances. Craige has studied the reactions of cows to intravenous injections of calcium salts.

Several stages of ventricular fibrillation are recognized. First there are premature ventricular beats, usually arising from multiple foci of hyperexcitability in the ventricle. Then comes a stage of tachycardia, which lasts a second or less. Next to develop is a condition, sometimes designated as ventricular flutter, in which there are irregular localized contractions accompanied by large electrical changes at a frequency of 600 or more per minute. In 15 to 40 seconds ventricular flutter passes into fully developed fibrillation. This "is characterized by multitudes of irregular yet forceful, shivering or trembling motions, each spreading very short distances and with highly variable frequencies over different surface regions" (Wiggers, 1944). The accompanying electrical changes are small and have frequencies of 1100 to 1700 per minute. After two or three minutes, as the effects of circulatory failure and anoxemia develop, the waves of contraction become weaker and travel more slowly.

In the stage of flutter intraventricular pressure is raised to some extent, but in the stage of fully developed ventricular fibrillation it is raised only very slightly.

Ventricular fibrillation does not involve the atria, these chambers continuing to beat in a normal manner.

It has been shown experimentally (Hooker, 1929) that fibrillation may be stopped by inhibiting the heart with potassium chloride. The inhibition is then overcome, and rhythmic contractions initiated, by use of calcium chloride. The action of calcium chloride is enhanced by the simultaneous use of adrenaline. The respective solutions are injected into the heart end of a carotid artery. Thus they are driven into the coronary arteries.

Further discussions of ventricular fibrillation may be found elsewhere (Hoff; Wiggers, 1944).

The Effect of Electric Shock on the Heart. An extensive study of this subject on animals has been made by Ferris and co-workers. Their standard conditions included the use of 60-cycle alternating current for a duration of 3 seconds. The electrodes were applied to the right foreleg and the left hind leg. They point out that current rather than voltage is the correct criterion of shock intensity. The average maximum current not causing fibrillation in the different species is shown in the accompanying table. In the smaller species (guinea pig, rabbit, cat) there was a tendency for the hearts to recover spontaneously from fibrillation. In tests on 500 sheep there was only one spontaneous recovery from ventricular fibrillation. (It is a well-known fact that in dogs spontaneous recovery is rare.) Electrocardiograms made during ventricular fibrillation were alike whether the fibrillation had been produced by direct current or alternating current. The heart was found to be most sensitive to fibrillation for shocks that were applied during the part of the ventricular cycle corresponding to the T wave of the electrocardiogram.

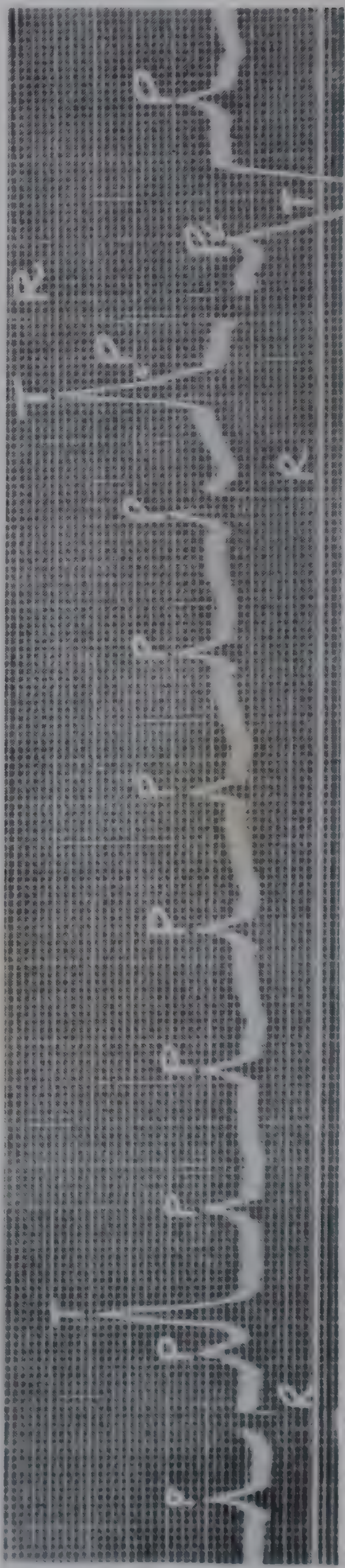

FIG. 41.—Electrocardiogram of a horse showing almost complete heart-block. The record shows numerous regularly spaced atrial waves (P) but only three ventricular complexes. The third ventricular complex probably arose under the influence of the normal pacemaker. (From Dukes, *Cornell Veterinarian*, 1940, 30.)

MAXIMUM 60-CYCLE CURRENT NOT CAUSING FIBRILLATION OF VENTRICLES
(Duration of shocks, 3 sec. Electrodes on right foreleg and left hind leg)

Species	Body Weight (av.)	Maximum Nonfibrillating Current (av.)
	kg.	*milliamp.*
Guinea pig	0.55	20
Rabbit	2.2	25
Cat	2.9	23
Dog	22	92
Pig	79	200
Sheep	56	240
Calf	70	270

(Data from Ferris and co-workers.)

These investigators found that fibrillation produced by an electric shock can usually be stopped and the heart be made to beat normally again by a subsequent electric shock of high intensity and short duration through the heart. For successful results the countershock must be applied quickly after the fibrillating shock.

As to man, Ferris and co-workers concluded as follows: "A current just below the threshold for ventricular fibrillation is the maximum to which man safely may be subjected. Based upon numerous tests on animals of several species comparable in size with man, this maximum current is about 0.1 ampere, for a duration of one second or more and a pathway between an arm and a leg."

Atrial Fibrillation. In this condition the atria show rapid, irregular, more or less incoordinated contractions which are of no value in emptying the chambers. They therefore become distended. The P waves of the electrocardiogram are absent, but fine electrical changes at a frequency of several hundred per minute are present. Atrial fibrillation can be produced experimentally by stimulating the atria with repeated electric shocks and in other ways. Although atrial fibrillation does not result in fibrillation of the ventricles, the latter chambers beat rapidly and irregularly. Atrial fibrillation induced by electrical stimulation often disappears shortly after discontinuing the shocks. However, it may continue for some time after the stimulation has ceased.

Atrial fibrillation may be preceded by a condition of atrial flutter. Here the beat is regular but very rapid.

A clinical condition of atrial fibrillation is common in man (Lewis, Wiggers) and is sometimes seen in animals (Roos, Batt). The clinical condition can be diagnosed by a study of the jugular pulse and of the electrocardiogram.

Chapter VI

THE FLOW OF BLOOD IN THE BLOOD VESSELS

THE BLOOD-VASCULAR SYSTEM

THE blood vessels of the body are of three main kinds: arteries, capillaries, and veins. Three types of arteries are recognized: elastic, muscular, and arterioles. Elastic arteries include the aorta, some of its large branches, and the pulmonary artery. Their walls contain much yellow elastic connective tissue. Muscular arteries contain a great deal of smooth muscle in their walls. Arterioles are small muscular arteries. Running from small arterioles directly to venules are arteriolovenular bridges, or thoroughfare channels, which are short circuits between the arterial and venous circulations. True capillaries are anastomosing branches of the main pathways from arterioles to venules. The bridges are always open to the circulation but the flow through the network of true capillaries is variable, being related to the activity of the tissues which they supply. Capillaries are made up entirely of endothelial cells but "precapillaries" show the presence of occasional muscle cells, known as Rouget cells, whose function may be to aid in controlling the size of the precapillary lumen. The capillaries next to the arterioles may be designated as arterial capillaries, those next to the venules as venous capillaries. Permeability in the region of the capillaries is apparently greatest in the venous capillaries and venules.

In addition to the above-described vascular arrangements in the region of the capillaries, there also exist *arteriovenous anastomoses.* These are direct connections, or shunts, without the intervention of capillaries, between arteries and veins. They are larger than capillaries, most of them having internal diameters of some 20 to 40 microns. They are present in birds and mammals, including man. In birds they occur especially at the base of the claws. In mammals they are found in the penis, at the base of the claws or hoofs or in the toe pads, in the ears, in the nose and snout, and other locations. They have been extensively studied by Clark and co-workers (Clark, 1938) in the ears of rabbits by means of permanently installed transparent windows.

They behave much as do arteries and arterioles, being capable of spontaneous contraction and dilatation. When dilated they allow a large quantity of blood to pass directly from artery to vein without traversing the capillaries. They probably assist in heat loss or the warming of peripheral parts by bringing larger amounts of blood to the surface. In other locations they probably have other functions.

The number of capillaries in the body is inconceivably great. Some studies by Krogh are of interest. This worker estimates that in a skeletal muscle fragment (horse) with a cross-section no larger than that of an ordinary pin (about 0.5 sq. mm.) there are some 700 parallel capillaries in addition to about 200 muscle fibers. In the dog the number of capillaries in a similar transverse section is nearly twice as great, but in the frog only about a third as great. The surface presented by 1 cc. of blood as it flows through the capillaries of the skeletal muscles of the horse is 7300 sq. cm.; of the dog, 5600 sq. cm.; of the frog, 2700 sq. cm. If all the capillaries in the skeletal muscles of a man could be placed end on end, the tube formed would reach around the world some two and a half times.

The *systemic circulation* conveys arterial blood from the left side of the heart to the body tissues generally, and returns venous blood from the tissues to the right side of the heart. The *pulmonary circulation* conveys venous blood from the right side of the heart to the lungs, where aeration takes place, and returns arterial blood to the left side of the heart. The *coronary circulation* is a part of the systemic circulation; it supplies blood to the heart itself. The term *portal circulation* is applied to the circulation of the portal blood through the liver. The portal vein receives venous blood from the capillaries of the stomach, intestine, pancreas, and spleen, and in the liver it breaks up into capillaries like an artery. These capillaries unite to form the hepatic veins, which open into the posterior vena cava. Therefore blood passing through the capillaries of the gastro-intestinal canal, pancreas, and spleen must pass through this second set of capillaries in the liver before it enters the posterior vena cava. The liver also receives blood from the hepatic artery. This is mixed with the portal blood in the liver.

HISTORICAL

In this complex system of vessels the blood is kept in continuous circulation mainly by the force of the heart beat. Strange as it may seem, the fact that the blood circulates, or moves in one direction only, has been known for only a little over 300 years. Some of the ancients believed that the movement of blood was of the nature of a circulation, but it remained for the English physician, William Harvey, to demonstrate experimentally that this is so. The results of his experiments were published in Latin, in 1628, and may be read in English in a number of translations.

MICROSCOPIC STUDIES OF BLOOD FLOW

Convincing evidence that the blood circulates may readily be obtained by microscopic studies of the blood movements in tissues of various animals such as the web of a frog's foot, the mesentery or bladder of small mammals, the mesentery even of the horse (Fåhraeus), the ear of the cat or rabbit, or the skin of man. Such studies also furnish information about the nature of the flow of blood in arterioles, capillaries, and venules. The blood flow in the vessels of the web of the frog's foot may be described briefly as follows.

The velocity in the arteries and veins is rapid, whereas in the capillaries it is slow. Pulsations are frequently seen in the arteries, but usually not in the veins and capillaries. However, in capillaries the flow is not always uniform; at times it may come practically to a stop. In the wider vessels the red blood corpuscles are usually found in the center of the stream moving comparatively rapidly; whereas the white blood corpuscles, much less numerous than the reds, are found at the periphery of the stream moving in an irregular manner. They tumble along, frequently coming to a standstill and apparently sticking momentarily to the sides of the vessel wall. They then detach themselves, move farther along, and again slow down or stop. The reason why the red corpuscles are drawn into the rapidly moving center of the stream and the white corpuscles are crowded into the nearly inert peripheral part of plasma is that there are differences in the size of the two classes of corpuscles; the red corpuscles of frogs are larger than the white corpuscles and are therefore drawn into the center of the stream. [In mammals the situation is said to be reversed: the white corpuscles, because of their large size, are drawn to the axis of the stream (Fåhraeus).] In capillaries it is seen that the corpuscles usually flow in single file because of the narrowness of the vessels. The blood flow in arterioles and venules is often so similar that it is hard to tell which kind of vessel is under observation. If the vessel can be traced to a point of bifurcation, a decision can be made; the flow in arteries is toward the point of bifurcation, in veins away from it.

Studies on the capillary blood flow in the kidney of the frog show that all the capillaries are not open at once; the flow is shifted from capillary to capillary and from glomerulus to glomerulus (Richards). Similar shifting has been noted in the capillaries of the skin of man and the ear of the rabbit (Krogh). In fact, it is now believed that, especially in resting tissues, many of the capillaries are closed, others only partly open, and still others widely open. As the tissue becomes active more capillaries open, thus increasing the blood supply. As previously noted, the arteriolo-venular bridges are always open to the circulation.

Observations on the blood flow in the arterioles and capillaries of the mammalian lung in the unopened chest have been made by Wearn and co-workers. The subject was the cat, which was kept under light but complete anesthesia. Through a window in the diaphragm the lower edge of the lung was transilluminated, and through a window in an intercostal space the circulation was observed with a microscope. Observations were made both in moving and in immobilized lungs. Blood flow in the arterioles was usually steady and nonpulsating, but at times it was pulsating. Changes from the nonpulsating to the pulsating flow and the reverse were commonly seen. Arterioles would appear and disappear. The wall of the capillary could not be seen but the flow of blood in the vessel could be followed. "The number of capillaries through which the blood flows at a given time varies greatly and may represent a very small fraction of the total number of capillaries in the lungs." Intermittence of blood flow in the capillaries was very commonly seen. Proof that the capillary wall could contract was not obtained. Variable results on blood flow were obtained with adrenaline. Pituitrin caused constriction of the arterioles. Histamine often caused closure of arterioles and capillaries.

THE FLOW OF A LIQUID IN TUBES

Before studying further the flow of blood in the blood vessels, it will be profitable to review briefly the flow of liquids in rigid and elastic tubes under different conditions of pressure.

In Rigid Tubes. If a reservoir containing water (or some other liquid) is connected at its base with a horizontal rigid tube, water will flow from the distal end of the tube in a steady stream, provided some means are taken to keep a constant level of water in the reservoir. If, as in Fig. 42, a series of vertical glass tubes are now connected at regular intervals to the horizontal tube, water will rise in each tube to a height corresponding to the side pressure of the water in the horizontal tube at the point where it is connected to the vertical tube. The side pressure as measured by any vertical tube is equal to the frictional resistance offered to the flow of the liquid from that point to the distal end of the horizontal tube, or is equal to the amount of pressure necessary to drive the liquid along the tube from the point of measurement to the outer end. Because the resistance is greater the farther the point of measurement is removed from the distal end of the horizontal tube, the column of water is highest in the vertical tube nearest the reservoir and lowest in the vertical tube farthest away from the reservoir. The pressure gradient, that is, the fall in pressure from tube to tube, is a straight line. The velocity of the liquid at any point in the horizontal tube is inversely proportional to the cross-sectional area of the tube or to the square of the radius. Therefore if the horizontal tube of uniform cross-sectional area is replaced by one whose area is not uniform, the velocity will vary from point to point.

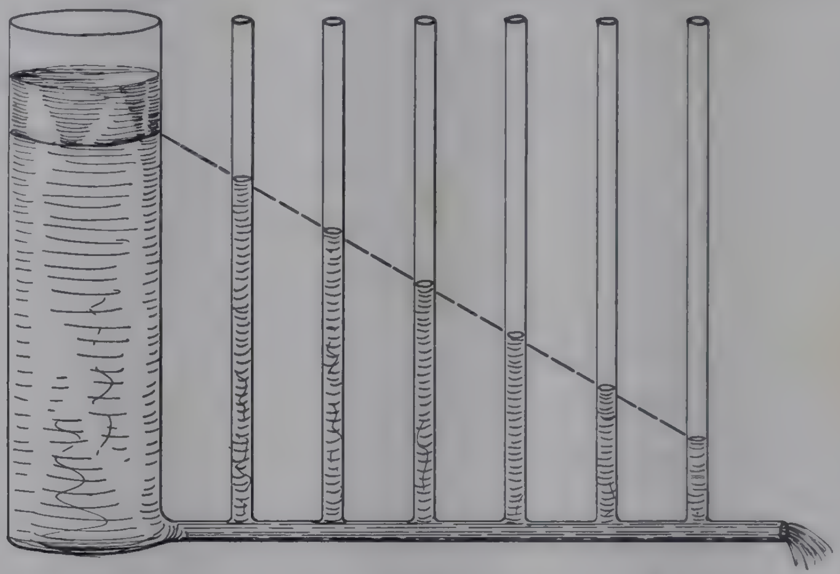

Fig. 42.—The flow of liquid in a rigid tube. The vertical tubes indicate the pressure at various points in the horizontal tube. The potential energy represented by the pressure of the heavily shaded portion of liquid in the reservoir imparts velocity to the liquid as it leaves the reservoir. It is termed the velocity head. The potential energy represented by the pressure of the lightly shaded portion of liquid is used up in overcoming frictional resistance. It is called the resistance head.

If the horizontal tube of uniform cross-sectional area is equipped with a partially closed stopcock situated somewhere along its course, the pressure in the proximal part of the tube will be increased and that in the distal part decreased (Fig. 43). Reducing the flow through the stopcock will cause the pressure on the left to rise and that on the right to fall. Increasing the flow through the stopcock will cause the pressure on the left to fall and that on the right to rise.

The mechanical arrangements just described are comparable, in some respects, to the blood-vascular system. The part of the tube from the reservoir to the stopcock represents the arterial system, the resistance offered by the partially closed stopcock represents the variable resistance encountered by the blood as it flows through the arterioles and capillaries (peripheral resistance), the part of the tube distal to the stopcock represents the venous system, and the nonuniform caliber of the horizontal tube signifies that the total cross-sectional area of the vascular bed is not the same in all parts. There are, however, some obvious differences between the system just described and the circulatory system: the flow of blood from the heart into the arterial system is not uniform but intermittent, and the walls of the blood vessels, especially the arteries, are elastic. In an effort to correct these differences, an intermittent pump may be substituted for the reservoir, and an elastic tube for the horizontal rigid tube.

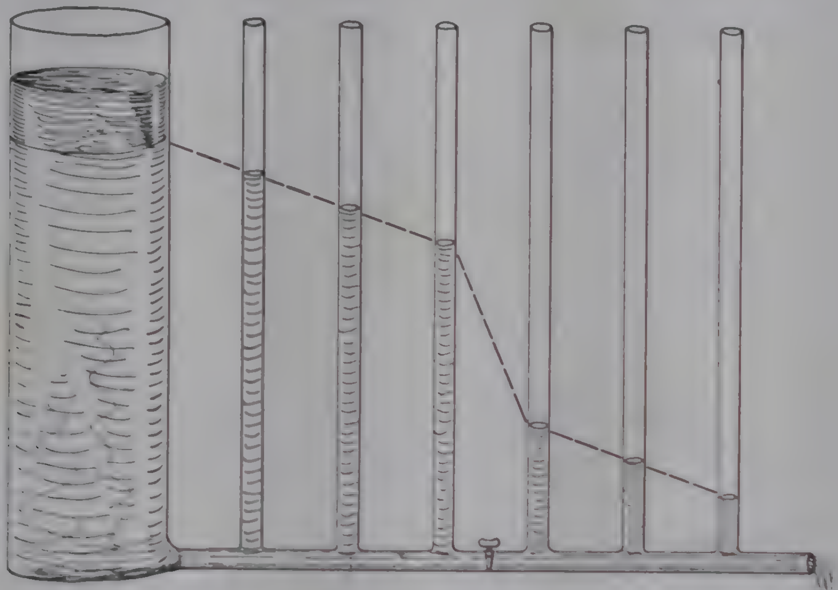

FIG. 43.—The flow of liquid in a rigid tube with high resistance at one point. The partly closed stopcock supplies the high resistance. The high pressure proximal to the stopcock and the low pressure distal to it correspond, in a way, to arterial and venous pressures, respectively.

In Elastic Tubes. If liquid is pumped intermittently into one end of a rigid tube, as much liquid must leave the distal end at every stroke of the pump as enters the proximal end, and the pressure in the tube must rise to a high point during action of the pump and fall to zero between strokes. No liquid will issue from the distal end of the tube between strokes. This is true even if the outlet of the tube is constricted (Fig. 44, *1*). If, on the other hand, liquid is pumped rhythmically into an *elastic* tube with resistance at the peripheral end, the intermittent flow from the pump is converted into a continuous flow from the other end of the tube; for a part of the force of each stroke is used to distend the wall of the elastic tube. The potential energy thus stored up manifests itself during the resting phase of the pump as kinetic energy of elastic recoil. In this way liquid is driven out of the far end of the tube in a continuous stream even during the idle phase of the pump, and the pressure in the elastic tube rises and falls rhythmically with the pump's action. These facts are illustrated in Fig. 44, *2*.

These systems illustrate certain mechanical features of the circulation, particularly in the arteries. It must be remembered, however, that the heart and blood vessels are a living, changing system and not a lifeless system of pump and tubes. It is quite impossible to reproduce mechanically all the characteristics of the circulation in the living animal, and a complete statement of all the physical laws involved in the circulation is at present impossible. There is no doubt, however, that the circulation of the blood obeys physical laws.

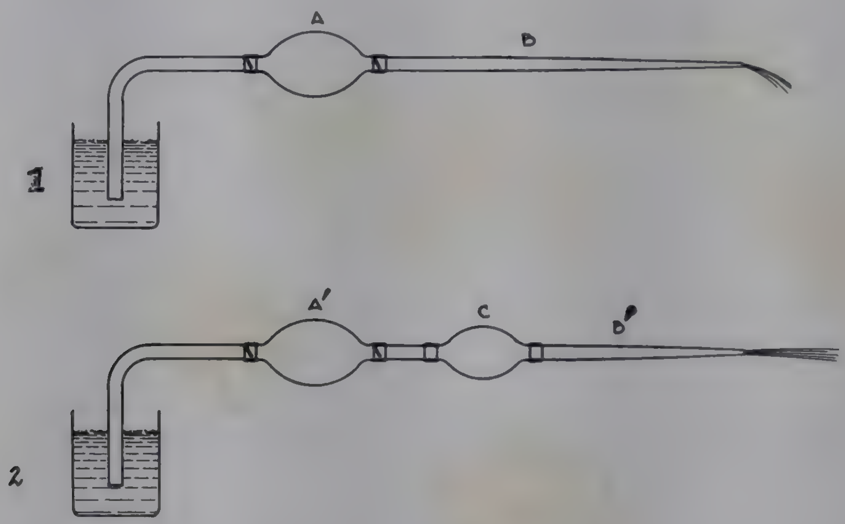

FIG. 44.—Diagrams illustrating the flow of liquid under intermittent pressure in rigid and elastic tubes. A, A′, rubber bulbs with valves; B, B′, rigid tubes; C, an elastic bag. Rhythmic compression of A results in an intermittent flow from the end of B. Rhythmic compression of A′ results in a continuous flow from the end of B′ because C, distended during compression of A′, recoils during the idle phase of the pump.

BLOOD VELOCITY

This may be considered from the standpoint of (1) the volume flow through different organs or regions, (2) the linear blood velocity, (3) the minute volume of the circulation, and (4) the circulation time.

The minute volume of the circulation and the circulation time are considered elsewhere (p. 100). The other two aspects of blood velocity will be dealt with now.

The Volume Flow. This may be measured in several ways. Ludwig's *stromuhr*, or "current clock," has been widely used. In its original form (Fig. 45), it consists of two glass bulbs (*a* and *b*) of equal capacity connected at the top by means of a tube which has an opening to the outside. Each glass bulb terminates below in a metal tube fixed into a round opening in a metal disk (p) which can be rotated through an angle of 180 degrees. Below this disk is a non-rotatable metal disk having openings immediately below the openings in the upper disk. Into the openings in the lower disk are fixed two tubes, c and c'. Through the opening to the outside in the tube connecting the bulbs, one bulb (a) is filled with oil and the other (b) with physiological salt solution or defibrinated blood. The blood vessel under consideration is clamped at two places and cut across between the clamps. Then the end closer to the heart, or, if the vessel is a vein, closer to the capillary area, is connected to tube c of the stromuhr and the other end of the vessel to tube c'. The clamps are removed from the vessel and blood is permitted to flow into bulb a. Thus the oil is displaced into bulb b and the salt solution or defibrinated blood from b into the distal stump of the blood vessel. When bulb a has been filled to the mark, and hence the oil has been expelled into bulb b and the salt solution into the blood stream, the bulbs are quickly reversed by rotation through 180 degrees and the procedure is repeated: blood is allowed to flow into b, displacing the oil into a and the blood from a into the blood stream. The bulbs are again reversed and the procedure is repeated a known number of times during a given period. If the capacity of each bulb is 10 cc. and the number of fillings has been 4 in one minute, then 40 cc. of blood have passed through the stromuhr in one minute. This represents the volume of flow per minute in the vessel under consideration. The method reveals only the average flow in a given time. The variations are not indicated.

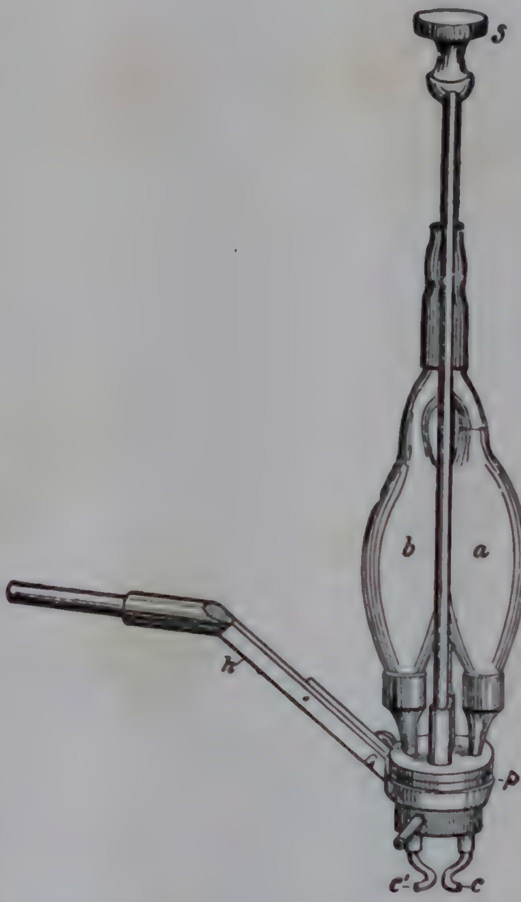

FIG. 45.—Ludwig's stromuhr. (From Howell's *Physiology*; copyright—W. B. Saunders Company.)

A modern development that enables volume flow to be measured in unopened vessels under nearly normal conditions is the *thermostromuhr*.

By means of a heating device placed in contact with the vessel, the blood, or more exactly the blood vessel, is slightly warmed. Thermojunctions above and below the heating element allow the differences in temperatures of the two points to be measured as galvanometric deflections. This temperature difference is approximately inversely proportional to the blood flow in the vessel. The instrument requires standardization. In the original method the heating was done with a high-frequency current and electrodes, but recently a thermostromuhr with a direct-current heater (Fig. 46) has been devised (Baldes and Herrick). The thermostromuhr method of measuring blood flow is thought to give

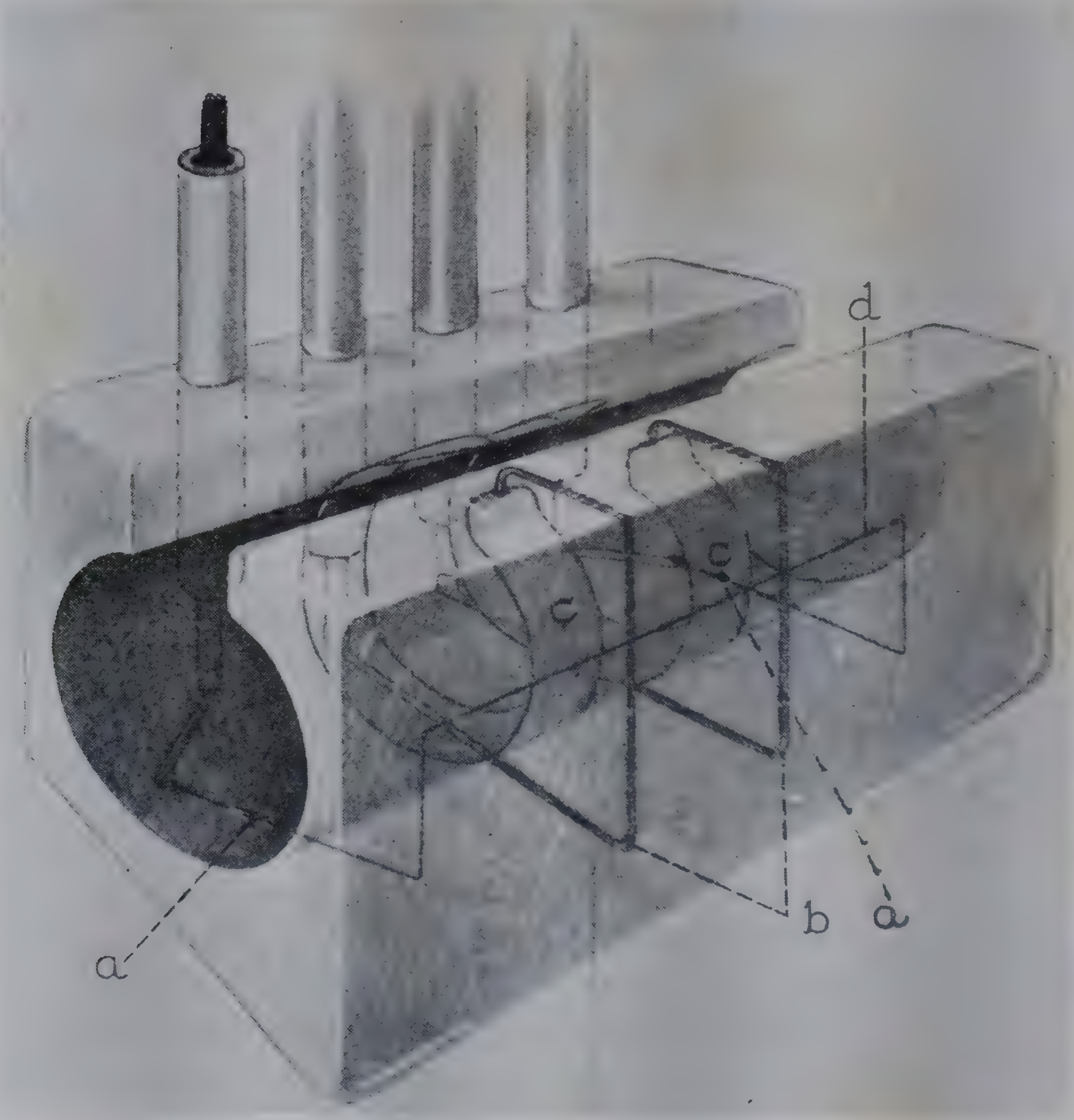

FIG. 46.—Thermostromuhr (enlarged): a,a, thermojunctions (copper and constantan wires soldered together); b, wires for the heating current; c,c, heating unit (nichrome ribbon) using direct current. The first and fourth wires at the back of the bakelite block lead to a galvanometer. The temperature difference between the two thermojunctions, recorded as galvanometric deflection, is approximately inversely proportional to the blood flow. (From Baldes and Herrick, *Proceedings of the Society for Experimental Biology and Medicine*, 1937, 37.)

accurate results. With aseptic surgical technic the unit can be left in place on the blood vessel for a long time.

An electromagnetic flowmeter has recently been used to measure volume flow of blood. It is based on the fact that an electromagnetic force is set up in the blood as it flows in a magnetic field (Kolin).

Results Obtained with the Thermostromuhr. Following are some results obtained by the Mayo Foundation workers on blood flow of dogs, by use of the thermostromuhr: Anterior mesenteric artery—before meal, 194 cc. per minute; after meal, 312 cc. (Herrick and co-workers, 1934). Hepatic artery, 45 cc. to 163 cc. per minute; portal vein, 252 cc. to 620 cc. (Grindlay and co-workers, 1941). Splenic artery, 97 cc. per minute; splenic vein, 91 cc. (Grindlay and co-workers, 1939). Femoral artery—normal, 77 cc. per minute; after sympathectomy on same side, 201 cc. (Herrick and co-workers, 1932).

Linear Blood Velocity. This refers to the distance traversed by the column of blood in a certain vessel in a given time. That the velocity of blood-flow varies in different vessels is proved by microscopic studies of the circulation. Such observations reveal that the velocity is rapid in arteries and veins and slow in capillaries. Furthermore, the simple operation of transecting an artery or a vein and noting the character of the hemorrhage therefrom shows that the flow from these vessels is rapid and suggests that the flow in the intact artery or vein is also rapid.

If the cross-sectional area of the vessel is known, the mean linear velocity can be calculated from the volume flow. Conversely the volume flow can be calculated from the linear velocity if the cross-sectional area is known. Assuming a volume flow of 80 cc. per minute (as determined by the stromuhr or thermostromuhr) in an artery 3 mm. in diameter, the calculation of mean blood velocity would be as follows:

$$\text{Mean velocity} = \frac{\text{volume}}{\text{cross-section}} = \frac{80{,}000 \text{ cu. mm./min.}}{1.5^2 \times 3.14} =$$

$$11{,}331 \text{ mm. per minute} = 189 \text{ mm. per second.}$$

There are several ways of measuring linear velocity directly. The hemodromograph, an instrument that works on the principle of the hydrometric pendulum, is now chiefly of historical interest. It was devised by Chauveau and was extensively used in blood velocity measurements in large animals. Because of its inertia it did not follow accurately the rapid changes in velocity occurring in the arterial stream. More modern methods include the use of differential manometers and of a resistance wire introduced into the blood stream.

Velocities in Arteries, Veins, and Capillaries. The blood velocity in *arteries* is not uniform. During systole of the heart there is a distinct increase (systolic velocity), whereas during diastole there is a decrease (diastolic velocity). This velocity pulse, caused by the intermittency of the heart's action, is more noticeable the closer the point of measurement is to the heart. As the periphery of the circulation—the region of the arterioles and capillaries—is approached, the velocity pulse gradually becomes less and less until in the region of the smallest arteries and capillaries it disappears; the flow is now uniform. That the flow in arteries is pulsating also may be demonstrated by the simple procedure of transecting an artery and watching the character of the hemorrhage therefrom. It is in spurts of the same rhythm as the heart beat.

Using the resistance-wire method, Machella obtained in dogs average velocities as follows: In the carotid artery—systolic velocity, 37 cm. per sec.; mean, 12.4; diastolic, 9.7. In the femoral artery—systolic velocity, 33.3 cm. per sec.; mean, 7.8; diastolic, 5.0.

On the whole, the velocity in *veins* is uniform, as is revealed by actual determinations and by cutting a vein across and watching the character of the hemorrhage. The rate of flow in the venous system increases as the heart is approached. It is slowest in the venules and fastest in the venae cavae at the heart, where, however, it is only about one-half as fast as in the aorta.

The methods of velocity measurement described above, while applicable to arteries and veins, are not applicable to *capillaries.* The velocity in these vessels may be measured microscopically in thin membranes. Such studies show that the capillary flow is, as a rule, nonpulsating. In the mesenteric capillaries of the dog a velocity of about 0.8 mm. per second has been observed; in the retinal capillaries of man it is estimated to be 0.9 mm. per second. It is probable that blood velocity in capillaries is nearly the same in all mammals. Since the total length of the capillary area through which a given particle of blood may travel probably does not exceed 0.8 mm., it is evident that the time spent in this area is usually not more than one second. During this time the necessary exchanges between the blood and the tissues must take place.

The mean velocity relations in different parts of the circulation are shown schematically in Fig. 47.

Differences in Mean Velocity Explained. As indicated above, the mean velocity in the arteries is great, gradually decreasing toward the periphery; it is slow in the capillaries; and it is rapid again in the veins, increasing from the capillary area toward the heart. The explanation of these differences is found in the fact that the mean velocity of blood flow at any point in the vascular system is inversely proportional to the total cross-sectional area of the bed at that point. When an artery divides into two branches, the cross-sectional area of the branches taken separately is smaller than that of the stem from which they arise, but their combined cross-sectional area is greater than the cross-sectional area of the parent vessel. Hence blood in arteries flows in a bed whose total cross-sectional area becomes gradually greater and greater as the periphery is approached. At the capillary area the bed undergoes a marked enlargement, the combined cross-sectional area of all the systemic capillaries being some 600 times the cross-sectional area of the aorta. Therefore the velocity in capillaries should be about 1/600 that in the aorta, and actual determinations indicate that such is approximately the case. In the veins, on the contrary, the blood flows in a bed whose cross-sectional area becomes smaller and smaller as the heart is approached. However, the total cross-sectional area of the venae cavae at the heart is about twice that of the aorta at the corresponding point; the velocity is therefore only about one-half as great. As regards velocity, the flow of blood in the blood vessels is comparable to the flow of water in a narrow stream that slowly widens and then suddenly empties into a lake, from which the water is drained away by a stream that is at first wide but gradually becomes narrow.

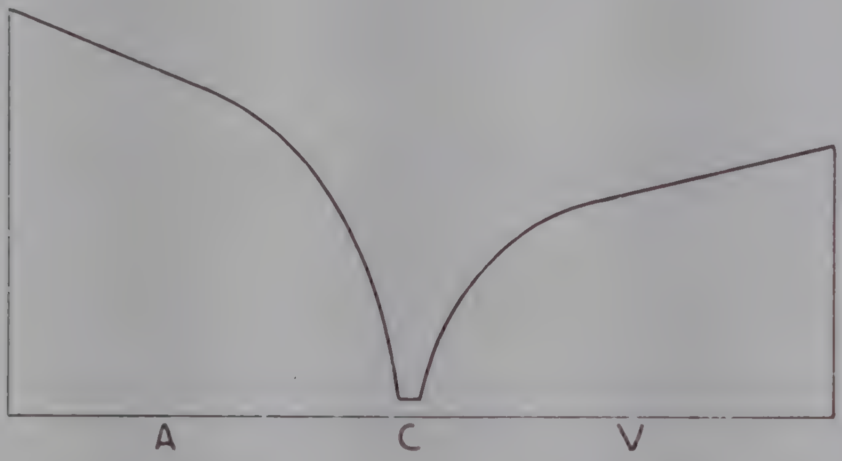

Fig. 47.—Diagram illustrating mean velocity relations in different parts of the circulation. A, arteries; C, capillaries; V, veins.

BLOOD PRESSURE

That the blood is under pressure and that this varies in different parts of the circulatory system is indicated by the following facts: (1) If an artery is cut across, the blood flows from the central end under high pressure and in spurts; if a vein is cut across, the flow from the peripheral end is rapid but under low pressure and without pulsations; if only capillaries are opened, the hemorrhage from the wound is under low pressure. (2) It is an established fact that the blood flows from the heart through arteries, capillaries, and veins back to the heart. From this it may be concluded that the blood is under pressure, and that there is a progressive fall in pressure from point to point throughout the circulation; otherwise the blood could not circulate. (3) Experiments on the circulation show that the blood is under high pressure in arteries, moderate pressure in capillaries, and low pressure in veins. The unqualified term blood pressure usually refers to arterial blood pressure.

Experimental Methods of Determining Blood Pressure. The most direct method of determining blood pressure is to connect a vertical glass tube to the vessel under consideration and see to what height the blood rises in the tube. Essentially such a method was employed by Stephen Hales, English clergyman and pioneer investigator of blood pressure in animals. His experiments were made in 1733 on several species of animals. In a horse the pressure in the crural (femoral) artery was equal to 8 feet 3 inches of blood. In another horse the pressure in the carotid artery was equal to 9 feet 6 inches of blood, and in the jugular vein to about 1 foot of blood. The method of Hales has a number of disadvantages such as the inconvenient length of the tube and the rapid coagulation of blood in the tube. It has therefore been improved and amplified, so that today there is available elaborate apparatus of a high degree of precision for determining and recording blood pressure. A simple method, shown schematically in Fig. 48, is to employ a U-tube (manometer) containing mercury, which is about 13 times as heavy as blood. The proximal limb of the manometer is connected through heavy-walled tubing to a cannula fixed in the blood vessel. Before establishing communication between the vascular system and the manometric system, one fills the latter with some salt solution—sodium citrate solution is commonly used—that prevents coagulation of blood. When the blood vessel is opened the blood gets no farther than the bulb of the cannula, its pressure being transmitted to the mercury through the incompressible liquid. The mercury in the distal limb of the manometer rises and that in the proximal limb falls until the columns balance the pressure of the blood in the vessel. A graphic record of the pressure may be made by using a recording manometer—one whose distal limb is provided with a delicate float, a standard, and a crossarm, which acts as a writing point—and a kymograph. The blood pressure equals twice the distance in millimeters from the base line (line of atmospheric pressure) to the tracing. (The distance is doubled because the manometer is a U-tube, that is, has two limbs.) The base line can be located by holding the open tip of the cannula at the level of the aorta. Tracings made with the mercury manometer, from the carotid artery of a pig and of a cow, are shown in Figs. 49 and 50.

Examination of an arterial blood pressure record made with a mercury manometer usually reveals two kinds of waves: long ones, which if observed during the making of the tracing are seen to be in rhythm with the respiratory movements; and short ones, synchronous with the heart beats. Both kinds of waves are very evident in Fig. 49; the respiratory waves are less evident in Fig. 50. The cause of the respiratory waves is discussed in another place (p. 209). The short waves are caused by the diastole and systole of the heart, and an examination of a blood pressure tracing shows that the amplitude of these waves is entirely too small. They manifestly are not an accurate picture of the diastolic and systolic pressure changes in the arteries. The explanation as to why the mercury manometer so imperfectly records rapid fluctuations in pressure is the inertia of the mercury; the latter

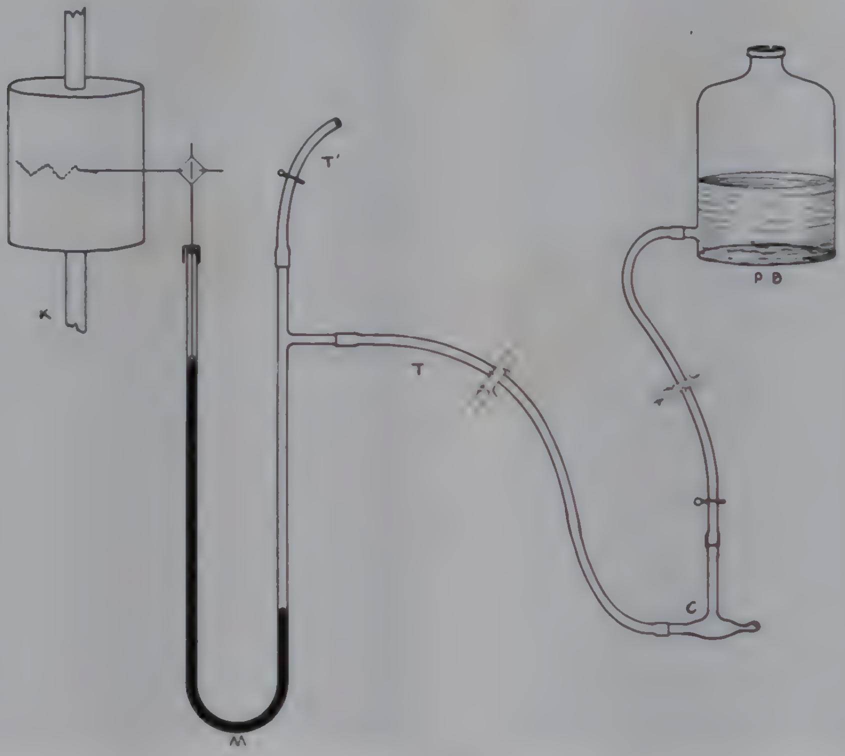

Fig. 48.—Diagram showing a method of taking a blood pressure tracing from an artery. K, kymograph; M, mercury manometer, carrying, on the left, a float, standard, crossarm, and writing point; T, heavy-walled rubber tubing connecting the proximal limb of the manometer with the arterial cannula C; P.B., pressure bottle containing anticoagulating solution—for example, sodium citrate; T', tube with a clamp for removing air or clots from the pressure system.

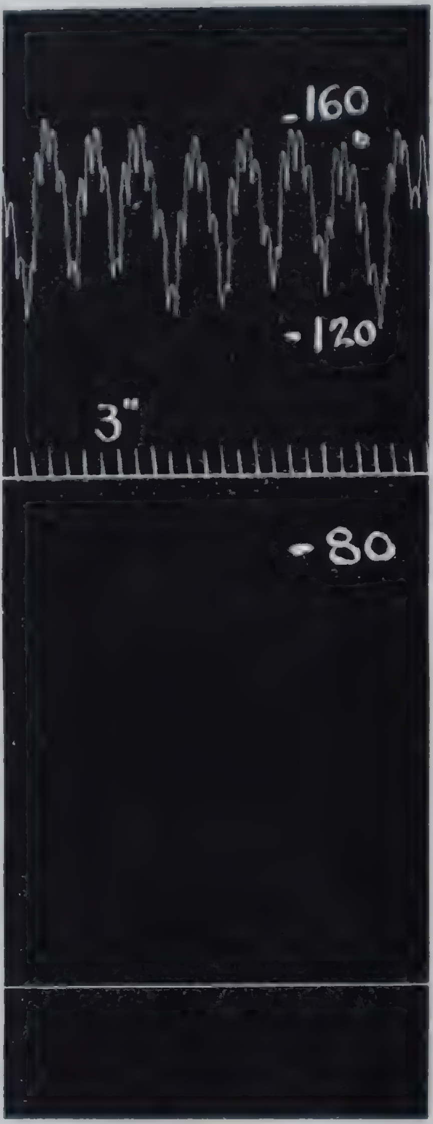

FIG. 49.—Blood pressure tracing from the carotid artery of a 19-kg. pig. Mercury manometer. Local anesthesia. The figures indicate the blood pressure in millimeters of mercury. The short waves of the tracing are caused by the heart beats. Their amplitude is much too small owing to the inertia of the mercury. The long waves are caused by the respirations.

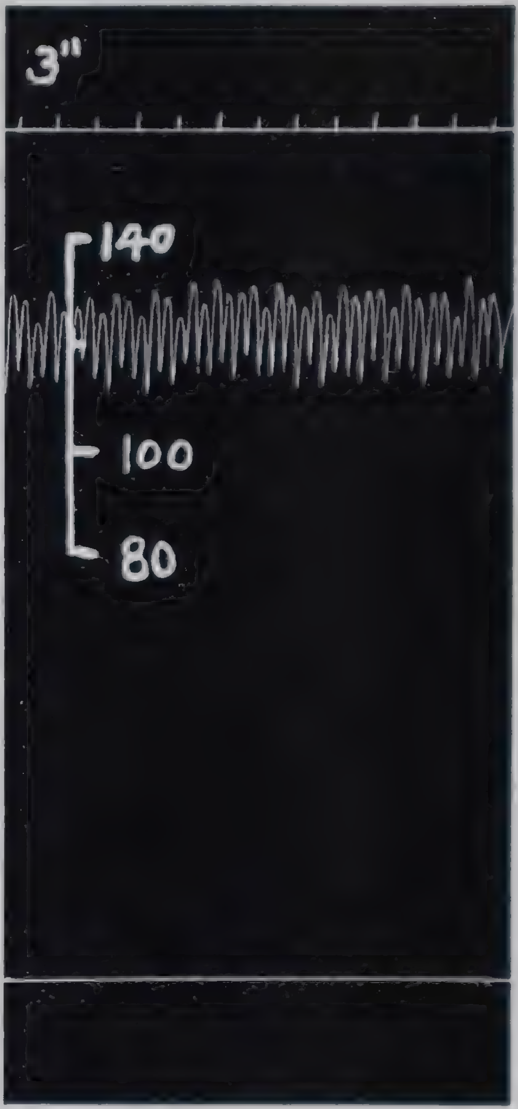

FIG. 50.—Blood pressure tracing from the carotid artery of a cow. Mercury manometer. Local anesthesia. The respiratory waves of blood pressure are less evident than in Fig. 49. It may be noted that the blood pressure of the cow was lower than that of the pig. For a graphic record of the blood pressure of a horse, see Fig. 33.

cannot completely follow rapid changes. It is able, however, accurately to follow slow changes in pressure, such as accompany the respirations, changes of posture, and the like. It should be kept in mind when studying a blood pressure record made with the mercury manometer that it is essentially a record of mean pressure and not of the extremes caused by the systole and diastole of the heart. This does not apply however, to mercury-manometer blood pressure tracings when the rate of the heart is slow—for example, in the horse normally or in small animals during vagus stimulation. The mercury is then able to follow the pressure changes. In fact, under such conditions the excursions of the mercury may be too extensive. Their amplitude can be damped by placing a partially closed clamp on the tube leading from the artery to the manometer (Fig. 33, p. 121).

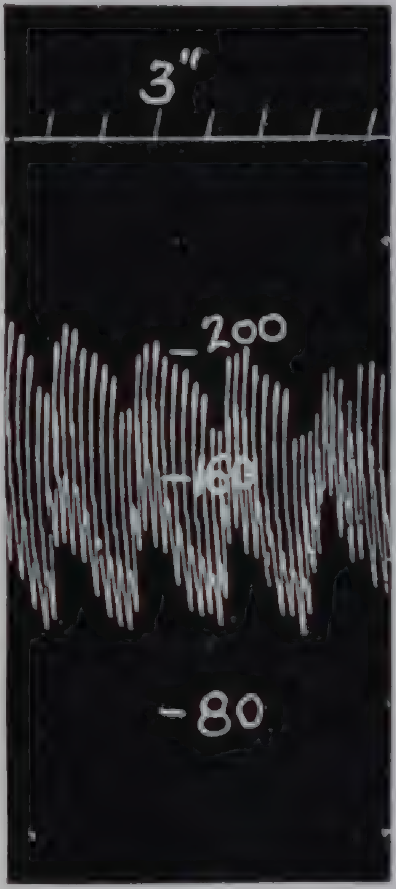

Fig. 51.—Blood pressure tracing from the carotid artery of a 43-kg. pig. Membrane manometer, calibrated in millimeters of mercury. Local anesthesia. The short waves are caused by the beat of the heart. Their amplitude is much greater than corresponding waves obtained with a mercury manometer. The long waves are caused by the respirations.

The inability of the mercury manometer to register accurately sudden pressure variations has led to the development of manometers whose sensitivity and natural frequency are great enough to record the details of a pulsating pressure. An early attempt in this direction was the membrane manometer. It consists of a small tambour which actuates a light lever. The capsule of the tambour is in communication with an inelastic tube leading to the artery. The capsule and tube are filled with liquid through which the blood pressure is transmitted to the membrane and thence to the recording lever. To get absolute values from the instrument, it is necessary to calibrate the movements of the lever. A blood pressure tracing made with a membrane manometer is shown in Fig. 51. Optical manometers (Wiggers, Green) are much better. In them friction and inertia of levers are entirely eliminated. Great sensitivity and a high natural frequency can be attained. The optical manometer is essentially a capsule whose membrane (rubber, metal, glass) actuates a small mirror attached to it. A band of light, produced by a suitable light source, is transmitted to the mirror which reflects the light onto a light-sensitive (photographic) surface moved by a photokymograph. The band of light is focused by means of suitable lenses or by use of a concave mirror.

Systolic, Diastolic, and Mean Arterial Pressures. The highest pressure attained in the arteries, which is synchronous with and due to the systole of the heart, is termed the *systolic pressure*; the lowest pressure, which occurs during diastole, is termed the *diastolic pressure;* the difference is known as the *pulse pressure.* In an artery that shows a systolic pressure of 140 mm. Hg, for example, the femoral of the dog, there is a diastolic pressure of about 80 and a pulse pressure of 60. By the *mean pressure* is meant the average pressure in a blood vessel over a given period of time. In arteries if the form of the pulse were a triangle, the mean pressure would be the sum of the systolic and diastolic pressures divided by two. Since, however, the form of the pulse is not a triangle, the true mean pressure cannot be obtained in this way. The arithmetical mean is nevertheless close to the true mean. The mercury manometer tends to trace a mean pressure (unless the heart rate is slow).

The pressure pulse disappears in the region of the arterioles. As the periphery of the circulation is approached, the difference between the systolic and diastolic pressures becomes less and less until in the region of the arterioles it disappears and the pressure becomes uniform. Because of the disappearance of the pressure pulse, the velocity pulse disappears in the same region. Also in capillaries and veins there is, usually, a nonfluctuating pressure and velocity.

Data on Arterial Pressure. The data in the table on p. 155 show mean arterial pressures in animals. The measurements were made with the mercury manometer. The values in the next table (p. 156), taken from a more extensive table of Woodbury and Hamilton, show heart rates and blood pressures in small mammals and birds. The records were made with an optical manometer. Examination of the figures in the tables reveals that the height of the blood pressure is a characteristic of the species rather than of the size of the animal. The blood pressure of the pig is as high as, and the blood pressure of the canary is higher than, that of the horse.

Capillary Pressure. Indirect determinations of capillary pressure, as by measuring the pressure necessary to blanch a portion of the skin or mucous membrane, did not yield satisfactory results. Much better results are obtained by direct measurement, in which a micropipette is introduced into the capillary and the pressure balanced against a column of saline solution. Using this method, Landis obtained the following average results in man: arteriolar capillary pressure, 45 cm. of water; venous capillary pressure, 22 cm. of water. These are pressures of approximately 34 mm. Hg and 17 mm. Hg. Lower pressures were found in the frog and pressures of intermediate value in small mammals (rat, guinea pig).

Venous Pressure. This can be determined experimentally with the mercury manometer. Because venous pressure is low and the displacement of mercury therefore small, salt solution or some other liquid may

MEAN ARTERIAL BLOOD PRESSURE (CAROTID ARTERY)

(The figures in parentheses indicate interindividual ranges of mean pressure).

Animal	Mean Pressure	Anesthesia	Remarks	Observer
	mm. Hg			
Horse	169 (152–194)	Local	Average of 6 animals 13–18 years old; good condition	Dukes & Sampson*
Cow	125	Local		Dukes & Emmerson*
Cow	166	Chloral hydrate		Dukes & Schwarte*
Calf	160–180	Nembutal	Several animals	Glenn, Muus, & Drinker
Sheep	110	Local	Average of 6 animals	Dresbach
Sheep	114 (90–140)	Local	Average of 13 animals ranging in weight from 27–133 pounds	Dukes & Sampson*
Goat	120	Urethane	Average of 4 animals	Dunn
Pig	169 (144–185)	Local	Average of 14 animals	Dukes & Schwarte
Dog	150	Local		Dukes & Sampson*
Dog	160	Local		Dukes & Sampson*
Dog	194	Local		Dukes & Sampson*
Dog	155 (120–176)	Nembutal	Average of 7 animals	Dukes & Sampson*
Cat	140–170	None	Indirect measurements of pressure in an exteriorized carotid artery	Liddell and Carleton
Cock	135		Average of 13 birds. Femoral artery	Kaupp

* Unpublished.

be used in the manometer instead of mercury. For purposes of comparison with pressures in other parts of the circulation, the results may be translated into millimeters of mercury. The accompanying data from the compilations of Tigerstedt and the experiments of Dunn (goat) and Riddle and Matthews (duck) are submitted as illustrative of venous pressure in different parts of the body and in different animals.

HEART RATE AND BLOOD PRESSURE OF SMALL ANIMALS

Animal	Average Heart Rate	Blood Pressure		Artery
		Average Systolic	Average Diastolic	
		mm. Hg	*mm. Hg*	
Mouse (2)	630	147	106	Carotid
Rat (2)	420	187	138	Carotid
Pigeon (4)	221	135	105	Brachial
Starling (2)	388	180	130	Carotid
Canary (4)	690	220	154	Carotid
Sparrow (1)	550	180	140	

These figures show that venous pressure is low, and that it is lower the nearer the heart is approached. In the great veins near the heart, in fact, it is negative, or below the pressure of the atmosphere, because

VENOUS PRESSURE

Animal	Vein	Pressure
		mm. Hg
Sheep	Left jugular	−0.1
	Right jugular	0.2
	External facial	3.0
	Internal facial	5.2
	Brachial	4.1
	Branch of brachial	9.0
	Crural (femoral)	11.4
Dog	Anterior vena cava, near atrium	−3.0
	Anterior vena cava, distal portion	−1.4
	Right external jugular	−0.1
	Left external jugular	0.5
	Right brachial	3.9
	Left facial	5.1
	Left femoral	5.4
	Left saphenous	7.4
Goat	Jugular (mean of 16 animals)	3.9
Duck	Brachial (mean of 4 birds)	4.4

of the negative pressure to which the mediastinal organs are subjected. Blood, therefore, is aspirated toward the thorax. The fall in venous pressure from the periphery of the circulation to the heart is said to be at the rate of 1 mm. Hg for every 35 mm. of distance. Experiments of Eyster and Meek (1930) show that venous and arterial pressures are relatively independent of each other, even when the arterial pressure changes are large.

Summary. Blood pressure, highest in the aorta, slowly diminishes in the arteries until the arterioles are reached, where the fall is sudden and marked. In the arteries there are large pulsations, which gradually disappear peripherally. The pressure in the capillaries, fairly low and usually nonpulsating, decreases toward the venous end. The venous pressure, low and nonpulsating, is lowest in the venae cavae at the heart and highest in the veins nearest the capillaries. Pressure relations in the circulation are shown graphically in Fig. 52.

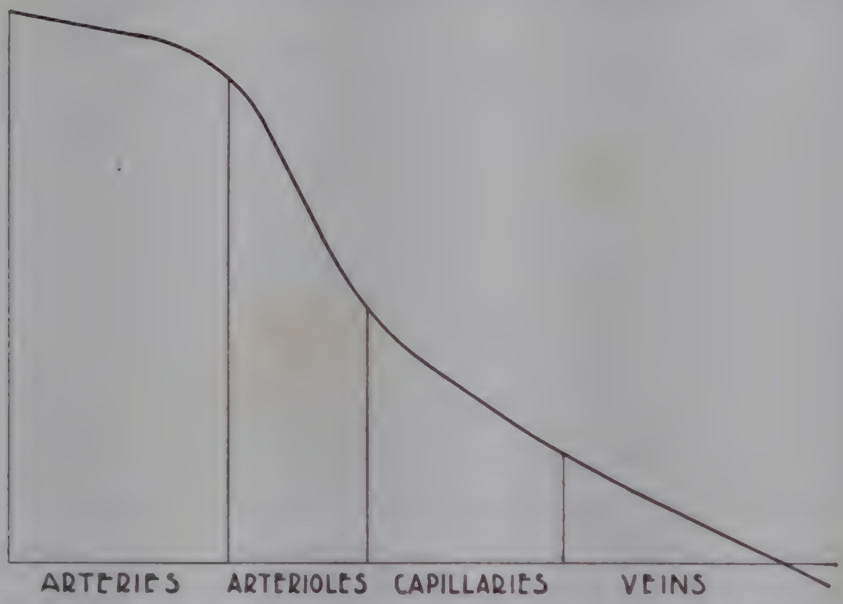

Fig. 52.—Diagram illustrating mean pressure relations in different parts of the blood-vascular system. Note the negativity of the venous pressure near the heart. The diagram does not accurately show the relative lengths of the different parts of the vascular system (arteries, arterioles, capillaries, and veins).

Clinical or Indirect Methods of Determining Blood Pressure. For such determinations in man adequate apparatus and technic have been developed, and the importance of blood pressure studies as an aid to diagnosis is universally recognized. In veterinary medicine, much less progress has been made in this direction. In large animals the relative inaccessibility of arteries of proper size has been an important limiting factor, and this difficulty has not yet been entirely overcome. A number of workers have made more or less successful attempts to determine the blood pressure in the intact superficial arteries (caudal arteries) of the horse and cow, but the technic has not yet received enough attention to cause its wide use clinically. A little more progress has been made in the dog and other small animals.

In blood pressure determinations the apparatus used is the sphygmomanometer. This consists essentially of a hollow compressing cuff, a manometer (mercury or aneroid), and an inflating pump, equipped with an exhaust valve. In man the cuff is strapped around the arm on a level with the heart, thus excluding the hydrostatic effect. By rhythmic compression of the bulb the cuff is inflated above the pressure necessary to obliterate the pulse as determined by listening to the arterial sounds by means of a stethoscope placed over the brachial artery at the cubital fossa (auscultatory method) or by palpation of the radial pulse (palpatory method). Then the cuff is slowly decompressed, and when the pulse reappears below the cuff, as determined by auscultation or palpation, the pressure is read. This reading represents systolic pressure. Deflation of the cuff is continued until the sounds given by the artery below the cuff show a characteristic muffling or disappear. At one or the other point the manometer is read, and the reading represents the diastolic pressure.

An uncompressed artery produces no sound. At certain stages of compression sounds are heard because of turbulent flow in the vessel below the region of compression. The auscultatory method, dependent upon these sounds, was introduced by Korotkov, in 1905, and the sounds bear his name. The systolic pressure can be determined more accurately by the auscultatory method. It is not possible to estimate the diastolic pressure by palpation.

In efforts to measure blood pressure indirectly in animals, some workers have used technics similar to those used in man, whereas others have made considerable modifications in the procedures. The auscultatory technic described for the dog by Rule is simple and should have ready clinical application. Systolic pressures of approximately 138 mm. Hg and diastolic pressures of approximately 79 mm. Hg were found. Wakerlin has described a relatively simple method involving the needling of a femoral artery. The method yields mean pressures, most of the values varying between 110 mm. Hg and 140 mm. Hg. Using the auscultatory method in dogs, Wakerlin found in the brachial artery an average systolic pressure of 140 mm. Hg and an average diastolic pressure of 90 mm. Hg. Other work on the dog has been done (Ferris and Hynes; Kolls; Allen; Deterling and Essex).

By means of a technic similar to that used in man, Covington and McNutt found that the normal systolic pressure in the middle coccygeal artery of the horse (224 animals) varied from 86 to 104 mm. Hg in different animals; it was somewhat higher in males. The diastolic pressure was 30 to 45 mm. Hg lower than the systolic. Fontaine found that the maximal pressure in the same location in the horse (120 animals) averaged 85 mm. Hg; minimal, 48 mm. Hg. None of these figures are corrected for the effect of gravity. Schilling has also reported results for the horse.

In lying cattle Götze found average pressures in the coccygeal artery as follows: maximum pressure, 202; minimum pressure, 136; pulse pressure, 66 cm. of water. When these figures are translated into millimeters of mercury, the following pressures are obtained: maximum, 149; minimum, 101; pulse, 49.

THE PRODUCTION OF BLOOD PRESSURE

Under normal conditions at least four factors co-operate in the production and maintenance of blood pressure: (1) the beat of the heart, (2) the peripheral resistance, (3) the elasticity of the arteries, and (4) the volume of blood.

The Beat of the Heart. The energy used to circulate the blood comes mainly from the beat of the heart. During systole of the heart the arterial pressure rises because the rate at which blood enters the arterial system exceeds the rate at which it drains through the arterioles into the capillaries. During diastole the pressure falls because of the passage of blood through the arterioles into the capillaries. If other conditions are unchanged, an increase in the rate or the amplitude (stroke volume) of the heart beat causes a rise of arterial blood pressure, whereas a decrease in the rate or amplitude causes a fall. If rate and amplitude vary in the opposite direction, their effects may cancel each other so that the blood pressure does not change.

According to the "peripheral heart" theory, active contraction of the large arteries aids in propelling the blood along the vessels. This theory was for a time supported by some workers. Wiggers (1923), who carefully reviewed the question, concluded that there is not only no evidence in favor of an "active systole" of the arteries but that its existence is incompatible with the slowness of smooth muscle contraction. On the other hand, Hooker said that it is quite probable, though by no means proved, that the capillaries and venules may supply some active force to the movement of blood, and Franklin expressed the view that the mesenteric veins in the sheep aid, by active contraction, in the flow of blood through the liver.

The Peripheral Resistance. As the blood flows through the blood vessels it encounters resistance to its movement. The resistance is largely an internal friction caused by the viscosity of the blood and is most noticeable at the periphery of the circulation, that is, in the region of the arterioles and capillaries. It is therefore a *peripheral resistance*. The exact seat of the peripheral resistance has been a subject of discussion. The older physiologists assumed that it was located in the arterioles, where the numerous vessels were constricted enough to offer distinct resistance to the rapidly moving blood. In the capillaries, however, the bed was so wide and the velocity of the blood flow therefore so small that the resistance was slight in spite of the small size of the individual vessels and hence the great frictional surface. Later work on the capillary circulation (Krogh, Richards, Wearn and co-workers) indicates that all the capillaries, especially in a resting organ, are not open at once. Some are widely dilated, some are completely closed, and some are partially open. The considerable blood velocity caused by this narrowing of the capillary bed, together with the small caliber of the individual capillaries, must result in resistance to the flow of blood. The conclusion seems justified, then, that some of the peripheral resistance lies in the capillaries. On the other hand, when most of the capillaries are open the peripheral resistance is not only decreased, but there is also a great increase in the *capacity* of the vascular bed, which tends further to reduce the blood pressure.

A general increase in peripheral resistance, other factors remaining the same, causes an increase in arterial pressure, and a general decrease in peripheral resistance causes a fall in arterial pressure. The regulation of the peripheral resistance will be studied in the next chapter.

The Elasticity of the Arteries. That the walls of large arteries contain a great deal of elastic tissue is well known. Because of the elastic recoil of the arterial wall, distended by blood during systole of the heart, a relatively uniform flow of blood is maintained in the capillaries during diastole. At the capillary area the nutrition of the tissues takes place; therein lies the chief importance of a uniform flow. Furthermore, the elastic arteries damp the blood pressure and thus protect the delicate capillary wall against sudden and great fluctuations of pressure, such as would occur if the arteries were rigid. When arterial elasticity is diminished the changes in arterial pressure becomes sharper, and it is possible that such changes may in part reach the capillaries. The relation of elasticity to flow is discussed also on p. 143.

The Volume of Blood. In general, the effect of an increased amount of blood in the circulation is to cause a rise in arterial blood pressure, whereas a decreased amount causes a fall. The degree of fall during hemorrhage depends on the rate of bleeding. If a large artery is opened there is an immediate though not marked fall, due chiefly to the sudden removal of a considerable amount of peripheral resistance when the cut is made. When, however, a small artery is opened there is at first no effect on blood pressure; it is only after a good deal of blood has been lost that a fall occurs. There are two principal reasons why there is no fall in blood pressure following moderate hemorrhage from small vessels: the vasomotor nerves cause constriction of the blood vessels and the spleen contracts (p. 47), forcing some of its store of blood into the general circulation. The effect of hemorrhage is further discussed on p. 64.

EXPERIMENTAL HYPERTENSION

It was shown originally by Goldblatt and co-workers (1934), and has been confirmed by many other investigators, that partial constriction of the main renal arteries by means of suitable clamps produces persistent hypertension. The original work was done on dogs, and most of the subsequent experiments have been made on this animal. However, researches reveal that other species, including sheep and goats (Goldblatt and co-wrkers, 1943), respond similarly to the dog when the renal artery is partially constricted.

The elevation of blood pressure following application of the clamp to the renal artery usually begins in 24 or 48 hours. The effect of the clamp is to lessen the flow of blood to the kidney, thereby causing some disturbance in the dynamics of the renal circulation. The exact nature of the resulting change in the renal circulation has not been determined.

In most dogs unilateral constriction of the main renal artery results in temporary hypertension which returns to normal in six weeks or less. In such hypertensive animals if the clamp is taken off the artery, allowing the circulation to the kidney to return to normal, or if the kidney with the constricted artery is removed, the blood pressure falls to the preoperative control level in 24 hours or less. In goats and sheep, and occasionally in the dog, constriction of one main renal artery results in hypertension which lasts for many months. In these animals surgical removal of the kidney with the constricted artery causes the blood pressure to drop to normal in 24 hours or less (Fig. 53). In dogs, sheep, goats, and other animals, constriction of both renal arteries results in hypertension of an enduring nature.

The *mechanism* of experimental renal hypertension has been extensively studied. That vasomotor reflexes (Chapter VII) are not involved is indicated by the observations that neither sympathectomy, partial or complete, nor complete destruction of the spinal cord will prevent or abolish the hypertension caused by constriction of a renal artery. Experiments have failed to reveal any causal relationship between the endocrine system and the hypertension.

There is a large body of evidence (see the review by Goldblatt and the book, *Experimental Hypertension,* 1946) that a chemical substance (humoral agent) produced by the kidney acts upon a substrate in the blood to produce a pressor, or blood-pressure-elevating, principle. The main facts may be summarized as follows:

Renin (an enzyme produced in the kidney) enters the general circulation via the renal vein and acts upon a substance known as *renin-substrate* or *hypertensinogen* (a component of the α_2-globulin fraction of the blood) to form *angiotonin* or *hypertensin* (a peptide), which is the vasoconstrictor substance. Angiotonin can be inactivated by *angiotonase* or *hypertensinase,* an enzyme present in blood and in extracts of organs.

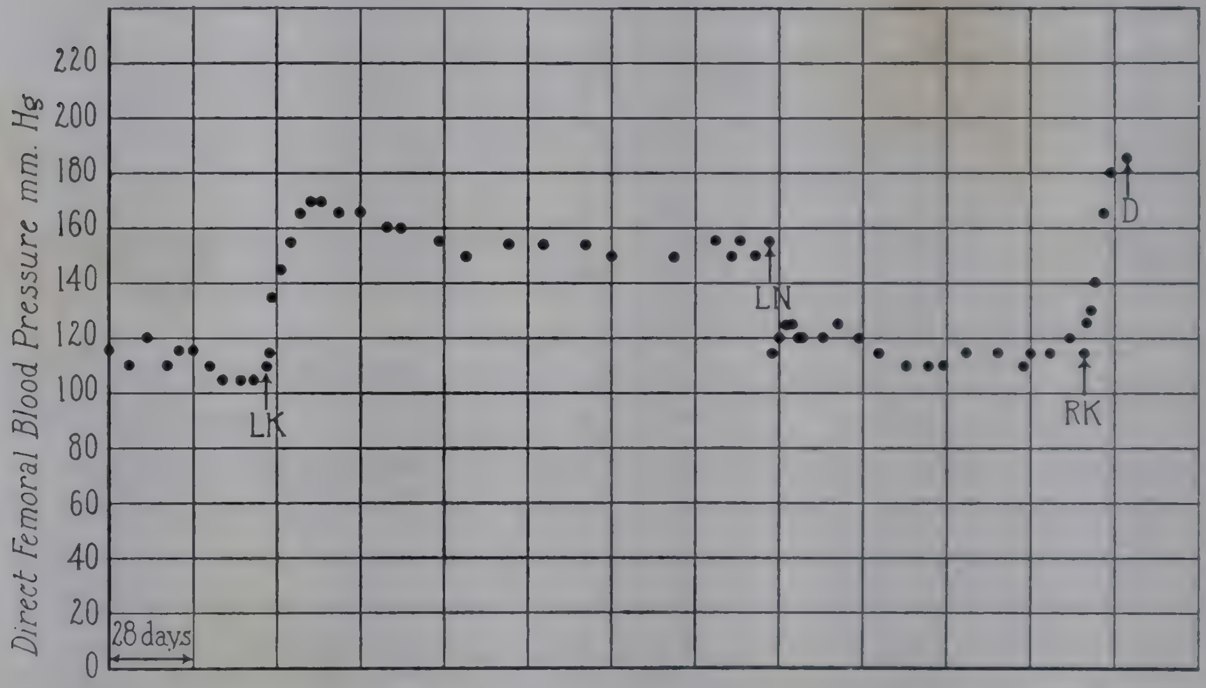

FIG. 53.—The development of experimental hypertension in a goat, female, age about 1 year. Blood pressures are mean values obtained by arterial puncture. At LK the left main renal artery was moderately constricted. Note that the blood pressure remained elevated for 6 months. At LN the left kidney was removed, whereupon the blood pressure fell to normal within 24 hours and remained there. At RK the right main renal artery was greatly constricted. The blood pressure rose again, but the animal developed uremia and died at D. Terminal blood findings: urea nitrogen, 134 mg. per 100 cc.; creatinine, 5.8 mg. per 100 cc.; CO_2 combining power, 40.5 volumes per 100 cc. (From Goldblatt, Kahn, and Lewis, *Journal of Experimental Medicine,* 1943, 77.)

The question naturally arises whether the humoral mechanism just described is concerned in the regulation of normal blood pressure. No definite answer can be given at present. There is recent evidence suggesting that the mechanism functions under normal conditions.

Renal hypertension, described above, is humoral in origin. A neurogenic hypertension of a persistent nature can be produced by bilateral denervation of the carotid sinus and transection of the aortic depressor nerves (Bing, Thomas, and Waples). For a discussion of the significance of the sinus nerves and the aortic depressor nerves in the regulation of the normal circulation, see pp. 125 and 183.

Essential Hypertension. This is a complex disorder in man, one of the most important manifestations of which is elevation of blood pressure due to an increase of peripheral resistance, which in turn results from increased vasoconstriction. It is not known to what extent this condition is of renal origin, although there is much evidence that experimental renal hypertension reproduces in many respects human essential hypertension (Goldblatt).

How frequently do essential hypertension and other forms of high blood pressure occur clinically in animals? It is generally assumed that hypertension is much less common in animals than in man, but there is actually no strong basis for this view, since few clinical studies of blood pressure in animals have been made. For a discussion of the problem as related to dogs, reference to the paper by Wakerlin may be made.

AIDS TO THE FLOW OF VENOUS BLOOD

The force of the heart beat is the chief factor causing the blood to circulate. However, the venous return, especially during muscular work, is aided by several factors as follows: (1) Contracting muscles compress the veins, which are thin-walled, thus assisting in emptying them toward the heart. Back flow is prevented by the presence of numerous valves. (2) At every inspiration the negative pressure on the organs in the mediastinum is further reduced. The lowered pressure is transmitted through the thin walls of the veins of the thorax to the blood within them. In this way blood is actually sucked toward the heart at every inspiration. The positive venous pressure added to the negative pressure exerted by the thorax gives what has been termed the *effective venous pressure*. Illustrative figures may be cited. A positive pressure in the great veins near the heart of 6 mm. H_2O and a negative pressure in the thorax of 60 mm. H_2O would give an effective venous pressure of 66 mm. H_2O. The backward movement of the diaphragm during forced inspiration raises the abdominal pressure by compressing the viscera. This further assists in emptying the veins toward the heart. (3) Modern work seems to indicate that venules and certain veins may, by active contraction, aid in the flow of blood through them.

THE EFFECT OF GRAVITY ON THE CIRCULATION

In addition to the force of the heart beat (hydrodynamic effect), the effect of gravity on the pressure conditions in different parts of the circulation must be considered. This is often referred to as the hydrostatic effect. Above the level of the heart, the hydrostatic force opposes the hydrodynamic force in arteries but is added to it in veins. Below the level of the heart the opposite conditions prevail: on the arterial side the hydrostatic force is added to the hydrodynamic force, but on the venous side it opposes the hydrodynamic force.

Gravity ordinarily presents no serious problem to the circulation in quadrupeds in the natural position except those with long legs and with long necks used in grazing or browsing. In man in the upright position the effects of gravity are very considerable. Arterial pressures above the level of the heart show no effect of gravity, the pressure in the brachial or carotid artery being in the standing position as high as, or in some instances higher than, the pressure in the same location in the lying position. The compensation is effected by reflex constriction of the arterioles, especially in the splanchnic area. In the lower limbs of man, however, no mechanism exists for counteracting the hydrostatic effect on the arterial side. For example, the blood pressure in the brachial and posterior tibial arteries in the horizontal position is the same, whereas in the standing position the pressure in the posterior tibial artery is much higher. This lack of compensation for the effect of gravity is ordinarily not serious.

It is on the venous side of the circulation that the effect of gravity is more manifest. Several factors account for this. The pressure in the veins is low, the veins are thinner-walled and more baggy than the arteries, and the vertical distance (in man) through which the venous blood has to be lifted in order to return it to the heart is much greater than that through which arterial blood has to be moved above heart level.

Compensations in man for the hydrostatic effect on the venous flow are usually well developed. The factors are in general the same as those already outlined as aiding the venous return. Of particular importance in counteracting the effect of gravity on the venous flow is adequate contraction, or tonus, of the skeletal muscles. In some individuals this is lacking, and fainting soon occurs when prolonged, quiet standing is attempted. Under these conditions there is a marked decrease in the cardiac output because of diminished venous return (Mayerson, 1943). This results in a fall of arterial blood pressure and cerebral anemia.

In quadrupeds with long legs the effect of gravity on the venous return from the legs must be considerable, but adequate compensation ordinarily exists. For example, in the hind limb of the horse several of the veins are so located as to be readily compressed during muscular contraction, and they have numerous valves. During grazing in large herbivorous animals, the hydrostatic effect on the venous flow from the head is counteracted by contractions of the muscles of mastication. The great muscles of the shoulders, back, and rump of the large quadrupeds are in general above the level of the heart. Gravity therefore aids the venous return.

Orthostatic Circulatory Failure. This condition, also known as gravity shock, occurs in some animals when kept for a prolonged period in the vertical position with the head up. Unanesthetized rabbits so suspended become unconscious in 20 to 120 minutes, and many of them die 2 to 24 hours after return to the normal position. In such suspended rabbits there occurs a peripheral circulatory deficiency or failure, which is accompanied by inadequate oxidative processes in the tissues (Cole and co-workers).

Anesthetized dogs are usually able to withstand for relatively long periods the upright position without serious circulatory deficiency; however, when the carotid sinuses are denervated and the vagi cut, compensation disappears, the blood pressure drops to shock levels, and the chances of recovery are slight. The latter animals are very susceptible to slight hemorrhage, the removal of small amounts of blood often bringing on an irreversible circulatory failure (Mayerson, 1942, 1944).

THE PULMONARY CIRCULATION

Previous statements regarding the flow of blood have had particular reference to the systemic circulation. It now remains to study similar conditions in the pulmonary circulation. This circulation extends from the right ventricle to the lungs and back to the left atrium. The general plan of the pulmonary circulation being similar to that of the systemic, it would be expected that the same principles governing flow in the latter circuit would apply in the former, and in a general way the principles are the same. However, there are some well-defined differences in the two circulations, and these are reflected in differences in flow.

In the pulmonary circulation the blood flows in a bed which widens more rapidly and offers less resistance than in the systemic circulation. Therefore in the pulmonary circulation a relatively lower pressure prevails on the arterial side and a relatively higher pressure on the venous side of the circulation.

The compilations of Tigerstedt show that the mean pressure in the pulmonary artery of the rabbit averages 14; of the cat, 16; and of the dog, 23 mm. Hg. From the right ventricle of unanesthetized goats Dunn obtained results that indicate a mean pressure in the pulmonary artery of 18 mm. Hg. Colin (Tigerstedt, vol. 4) found a pressure of 33 to 58 mm. Hg in the pulmonary artery of the horse. Wiggers concluded that the systolic pressure in the pulmonary artery of the dog is about 40 mm. Hg, and the diastolic about 10 mm. Pulmonary arterial pressure falls on inspiration, rises on expiration. The same relationship usually holds in the systemic circuit (p. 209). Johnson and co-workers found that the velocity of the pulse wave in the pulmonary artery under normal conditions is about the same as in the aorta. These investigators noted that sudden changes of great magnitude in the systemic arterial pressure have only slight immediate effect on the pulmonary arterial pressure. This is explained in part by the fact that the pulmonary vessels can increase their blood content considerably with little change in blood pressure. That the blood vessels of the lungs can store a considerable quantity of blood is evident from several lines of work.

The lowness of the pulmonary arterial pressure indicates that pulmonary capillary pressure is below the osmotic pressure of the blood proteins. This probably explains why the alveoli do not contain fluid under normal conditions.

Deep-chested animals kept on the back for some hours may die. The cause of death in goats and sheep kept on the back has been studied by Greenberg and co-workers. Death was caused by severe pulmonary changes, which were revealed at autopsy. Pulmonary congestion, alveolar hemorrhage, and interstitial edema were noted. Gas in the rumen was not related to the development of the conditions that led to death. A possible explanation is that the weight of the heart pressing on the pulmonary veins might interfere mechanically with the return of blood from the lungs to the heart. Thus the pulmonary circulatory changes could occur.

Microscopic studies of the blood flow in pulmonary vessels are discussed on p. 140; the vasoconstrictor nerves of the lungs on p. 177.

THE ARTERIAL PULSE

From what has been said about the flow of a liquid in elastic tubes, a general idea of the cause and significance of the arterial pulse will have already been acquired. The pulse is a wave of expansion and elongation of the arterial walls produced by variations in arterial pressure during each beat of the heart. The pulse begins at the aorta, passes over the entire arterial system, and disappears, under usual conditions, at the periphery. The production of the pulse may be described as follows: When the ventricle contracts, blood is forced into an already full aorta. Since blood is incompressible, room must be made for the newly discharged quantity. This could be accomplished by moving the entire mass of blood forward and discharging into the right atrium an amount equal to that expelled from the left ventricle, or by a stretching of the arterial wall sufficient to accommodate the new amount of blood, or by a combination of these methods. Actually both adjustments take place, but the distention of the arterial wall is the more prominent. This distention, and recoil, beginning at the aorta, is transmitted from point to point in the wall of the arteries (Fig. 54). It constitutes the pulse or pulse wave. The pulse is therefore the transmission of a pressure change in the arterial wall and the blood as it flows through a system of elastic vessels. The wave of pressure increase, or pressure pulse, is accompanied by an acceleration of the blood flow (velocity pulse).

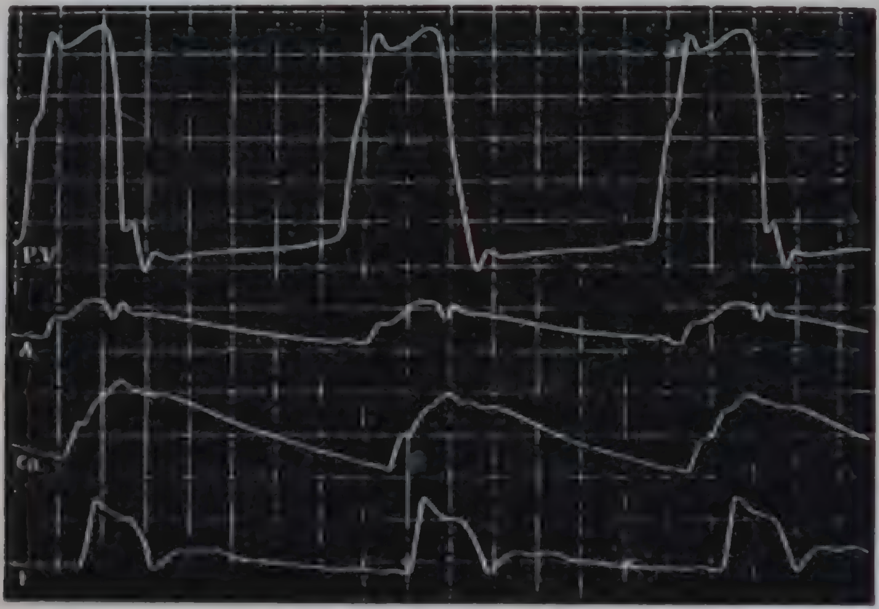

FIG. 54.—Simultaneous tracings (Marey, 1881) of intraventricular pressure (PV), aortic pulse (A), carotid pulse (Ca), and femoral pulse (F) in a horse. The vertical lines represent intervals of 0.1 sec. The pulses were recorded mechanically and doubtless contain artifacts due to inadequacies of the recording systems. Nevertheless they clearly show a number of important features including the lag in the appearance of the pulses.

Velocity. The velocity of the pulse wave should not be confused with the velocity of the blood current. The former velocity is much faster. In the arm arteries of man it is of the order of 7000 mm. per second, whereas the systolic blood velocity in a large artery is some 370 mm. per second — 19:1. The average velocity of the pulse wave may be estimated by measuring the difference in the time of the appearance of two pulses, for example, a central and a peripheral pulse, and then measuring the distance between the points at which the pulse records were taken. The pulses may be recorded by placing receiving tambours over the arteries and connecting the receivers with recording tambours arranged to write on a rapidly moving surface. A tuning fork or other time-marker also is arranged to write on the surface. The lever of the tambour recording the central pulse will be elevated before the one recording the peripheral pulse. The interval between the elevations will represent the time required for the pulse wave to travel through the arterial system between the two points. Assuming that the distance between the points over the arteries is 75 cm. and the time required for the pulse to travel the distance is 0.1 second, the average velocity of the pulse wave (distance/time) is 75 ÷ 0.1 = 750 cm. = 7.5 meters per second.

The pulse wave may be more accurately recorded by replacing the ponderous levers of the recording tambours with little mirrors fixed to the rubber membranes. A band of light is projected onto the mirror and the movements of the reflected band, which correspond to the oscillations of the membrane, are recorded on a moving photographic surface. A concave mirror makes unnecessary the use of lenses in the optical system.

In another method of measuring the velocity of the pulse wave, the pulses exert pressure upon delicate microphones whose potentials when amplified activate delicate galvanometers. The galvanometric deflections are recorded on a photokymograph.

The velocity of the pulse wave varies in different arteries. It is much slower in the large central arteries than in the smaller peripheral ones. Fair figures for the arteries of man are as follows: arteries near the heart, about 3 meters per second; arm arteries, 6 to 8 meters per second; leg arteries, as much as 13 meters per second.

In general, the more rigid the artery the faster the pulse wave travels, whereas the more elastic the artery the slower it travels. Differences in arterial elasticity are responsible in part for the differences in pulse wave velocity in central and peripheral arteries. In arteriosclerosis the pulse wave may be found to travel at a greater velocity than normal, whereas in aneurysm of the aorta it travels at a lower velocity. The velocity variations in arteries of different degrees of elasticity will be clearer when it is considered that the travel of a pressure change in a rigid tube is practically instantaneous, whereas in an elastic tube appreciable time is required for the transmission of the pressure change.

Length. The length of the pulse wave is very great. It may be calculated by multiplying the velocity by the period of the wave, that is, the time required for the wave to pass a given point. This time is the same as $\frac{\text{60 sec./min.}}{\text{pulse rate/min.}}$. Assuming a velocity of 7 meters per second and a pulse rate of 75 per minute, the length of the pulse wave would be 7 m./sec. × 0.8 sec. = 5.6 meters. Evidently the pulse wave reaches the most outlying arteries before it disappears at the root of the aorta.

Form. The form of the pulse wave is studied by means of graphic methods. Several methods of obtaining graphic records of the pulse have already been indicated. Another method requires the use of an instrument known as a sphygmograph. Many kinds of sphygmographs for application to man have been devised, and most of them are so constructed that they can be fastened to the arm near the wrist so as to give a record of the radial pulse. The impact of the pulse activates a small buttonlike structure whose movements are transmitted through a system of delicate magnifying levers to a writing point. This traces a curve on a piece of smoked paper made to move by clockwork. A time-marker is usually provided. Mechanical sphygmographs of this kind are not now much used in accurate work. The inertia of the writing levers is too great.

The record of the form of the arterial pulse is a curve known as the sphygmogram. It may be divided into two fundamental parts, systolic and diastolic, which are separated, on the descending limb, by a notch. In central pulses this is known as the *incisura* and in peripheral pulses as the *dicrotic notch*.

The incisura signals the closure of the aortic valve. It is caused by a sudden increase in the capacity of the aorta when the aortic valves, upon closure, bulge back somewhat into the relaxing ventricle. The incisura is followed by one or more oscillations.

As the incisura passes peripherally as a component of the pulse wave, it undergoes modification to form the dicrotic notch of peripheral pulses. One of the principal factors in bringing about this modification is the reflection of waves back from the arterioles because of the increased resistance to flow that occurs in this region of the circulation. Small vibrations may precede and follow the dicrotic notch.

The ascending limb of the pulse curve is known as the *catacrotic limb*, the descending the *anacrotic*. In central pulses a bend or shoulder is usually seen on the upper part of the anacrotic limb, but this is not commonly seen in peripheral pulses. The anacrotic bend results from the distention of a greater zone of the aorta by the ejected blood as the pulse wave travels.

Actually the factors involved in the production of the pulse wave and the change in form which it undergoes as it travels peripherally are much more complex than the brief description given here would indicate. Fuller discussions and detailed analyses may be found elsewhere (Wiggers, 1944; Hamilton).

Palpation. The pulse may be palpated in many of the superficial arteries, the ones most accessible varying in the different species. In the horse the external maxillary artery is the one commonly used, although others are accessible. In the cow the same artery or the saphenous may be used. In the sheep, goat, dog, and cat the femoral artery is the most accessible. In the pig palpation of the pulse is difficult or impossible; hence it is customary to count the number of heart beats by palpation or auscultation over the cardiac region. Palpation of the pulse gives to the experienced examiner valuable information about the heart and circulation. Thus the heart rate, at least the ventricular rate, is usually readily determined. (However, premature ventricular beats occurring near the beginning of diastole may not eject enough blood to produce a detectable peripheral pulse.) Whether the pulse is rhythmic or arrhythmic is also noted. The amplitude or size of the pulse can be estimated. The form of the pulse gives information about the speed with which the wave rises and falls and about the relative duration of the systolic and diastolic phases. A rough estimate of the blood pressure can be made by pressing on the artery.

VENOUS PULSE

The arterial pulse usually disappears at the periphery of the circulation. When, however, the peripheral resistance is much relaxed, the pulse wave may pass across the capillaries, appear in the veins, and so constitute a venous pulse. However, the term venous pulse as commonly used has a different meaning from this and refers to a pulsation in the large veins near the heart, often visible in some animals over the jugular veins in the region of the neck. Among domestic animals it is best seen in the ox (dairy cows) for the reason that in this species the jugular veins and anterior vena cava are comparatively large (Malkmus). A graphic record of the venous pulse shows a number of waves, some positive and some negative (Fig. 55). The first of these, the *a* wave, is positive and is due to atrial contraction, following which there is a negative wave due to atrial relaxation. Another positive wave, designated the *c* wave, now occurs. It is attributed mainly to the pulse in the underlying carotid artery and to the aortic pulse causing a pressure change in the large veins. However, there is at the beginning of ventricular systole a positive wave in the atrium caused by the bulging of the closed A-V valve into this chamber, which probably enters into the production of the *c* wave. There now follows another negative wave believed to be produced by the downward movement of the closed A-V valve and the consequent lengthening of the atrial cavity when the papillary muscles shorten in systole. Next comes a third positive wave (*v*) due to the gradual filling of the atrium during ventricular systole. This wave is followed by a third negative wave caused by a fall in pressure in the atrium incident to the discharge of its blood into the ventricle when the A-V valve is opened. From this discussion it is evident that the jugular veins act as a kind of manometer showing pressure changes in the right atrium. It is also obvious that the rate of atrial contraction can be determined from the venous pulse.

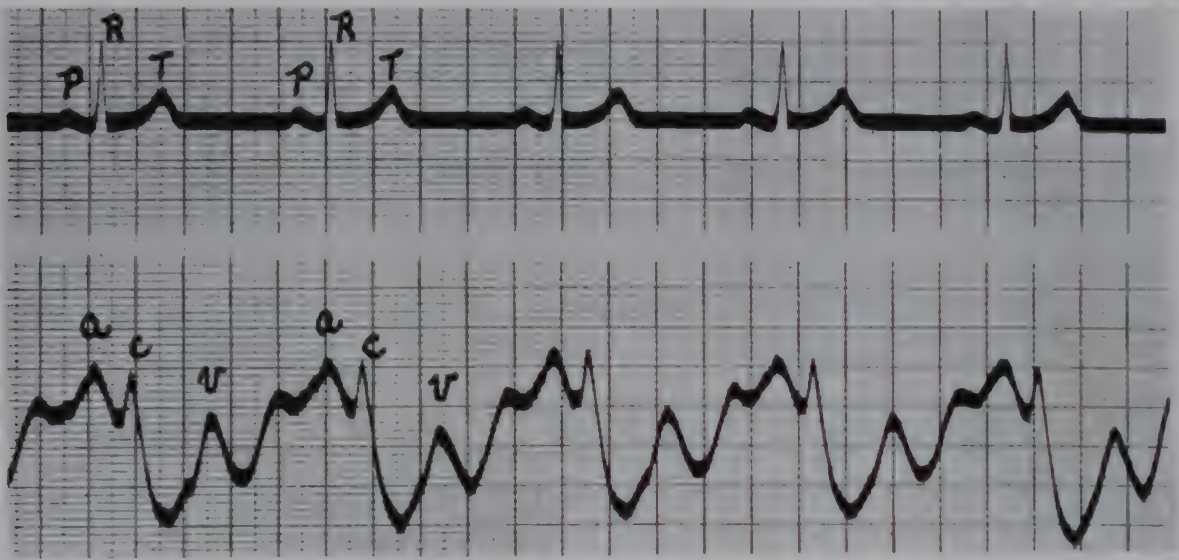

FIG. 55.—Simultaneous electrocardiogram (lead II) and record of jugular pulse of a man. The jugular pulse tracing was made by the use of a crystal microphone for receiving the pressure variations and a string galvanometer. Time, 0.1 sec. and 0.2 sec. There is a slight lag in the components of the jugular pulse tracing in comparison with the electrocardiogram because of the transmission time from the heart to the point over the jugular vein at which the pulse was detected. (From Miller and White, *American Heart Journal*, 1941, 21.)

The components of the venous pulse described here apply to man. There is no doubt, however, that the mechanism of the production of the venous pulse is similar in all normal animals. A fuller discussion of the venous pulse, and the literature, may be obtained elsewhere (Lewis, Wiggers).

Pathological venous pulses may occur. Tricuspid stenosis and tricuspid insufficiency result in abnormal pressure waves in the great veins; but the time of their appearance in relation to the events of the cardiac cycle is not the same. Many other cardiac abnormalities give rise to alterations of the venous pulse.

SHOCK

This is a very complex problem toward the solution of which a great deal of work has been done. The study of shock was greatly accelerated as a result of World War II. During the war years over 2000 papers on the subject appeared, at least 800 of which were of an experimental nature (Gregersen).

Signs of severe shock (dog) are: "Extremities cold, skin bloodless, peripheral veins collapsed, oral mucous membrane dry and pale, thirst, lack of sensitivity to pain, and central nervous depression bordering on coma" (Gregersen). Wiggers (1942) in reviewing the shock problem emphasized the circulatory impairment which "steadily progresses until it eventuates in a state of irreversible circulatory failure."

Two principal methods of producing shock have been employed in recent experiments: trauma and hemorrhage. Some of the forms of trauma that have been used (under anesthesia) are a tourniquet applied to one or more extremities and later released, crushing, compression, muscle contusion, and injury to intestinal loops. In unanesthetized dogs a massive hemorrhage which reduces the blood volume some 40 to 50 per cent will result in severe shock.

Studies continue to be made in an effort to find a toxic factor in shock. Some of the toxic substances that may be involved or that have been used in these experiments are histamine, continuous injections of adrenaline, peptone, bacterial toxins, tissue extracts, and blood from shocked animals.

Stimulation of afferent nerves has not been shown to result in shock except in rabbits, in which long-continued stimulation of the aortic nerves leads to death from circulatory failure. It is possible, however, that an afferent nervous factor is involved in some forms of shock.

The primary factor in the cause of shock (traumatic and hemorrhagic) appears to be a large reduction of blood volume. This occurs at the time of injury. "Hence, contrary to earlier concepts, the gradual failure in the circulation, at least in these two forms of shock, cannot be ascribed to a gradual decrease in blood volume" (Gregersen). Recent work has also shown that in traumatic shock the reduction in blood volume occurs as a result of fluid loss into the damaged area and not—as was formerly held—as a result of generalized capillary leakage.

If the progressive circulatory failure which characterizes shock is not due to a *progressive* decrease in blood volume, it is proper to inquire where the physiological defect occurs. It is the cardiovascular apparatus that fails. At the time of the trauma and blood loss, the cardiac output falls sharply. Then there is a progressive decline to as low as 10 per cent of the normal values. The mean blood pressure is also much reduced. There is evidence which suggests that vasodilatation in the muscles may be a factor in the terminal stages of shock. Accompanying the changes in circulatory dynamics in shock, there are other physiological and metabolic derangements. Pulmonary ventilation is increased, oxygen consumption is decreased, the arteriovenous oxygen difference is markedly increased, severe acidosis develops, and a condition of stagnant anoxia prevails. Urine secretion is slight or absent, and the nonprotein nitrogen of the blood increases. The hemodynamics of shock are analyzed in a recent review by Wiggers (1947).

Although a reduction in blood volume is the primary factor in the cause of shock, there is evidence that blood volume reduction is not the only cause of death in traumatic shock. The mortality rate in animals suffering from traumatic shock is several times higher than that in animals showing shock from simple hemorrhage (Gregersen and coworkers). Additional factors are evidently concerned, but researches have not revealed what they are. Following are possibilities: toxic factors, afferent nervous factors, and infection. In respect to the last suggestion, it has been shown in recent studies that clostridia, present in the normal tissues of dogs, may under some experimental conditions cause toxemia. During periods of circulatory insufficiency bacteria normally present in the alimentary tract may enter the blood stream. It has been suggested that the circulatory failure of infectious diseases may be caused or aggravated by bacterial toxemia.

Experimental shock produced by trauma and hemorrhage resembles clinical shock seen after these conditions.

In the *treatment* of shock the restoration of blood volume is of first importance, and the use of blood or blood substitutes (p. 65) has been much studied. Pressor substances and heart stimulants have been found of doubtful value or ineffective. Cooling of traumatized parts affords protection against shock. Infusions of sodium bicarbonate have been found helpful in counteracting the acidosis which is apparently a factor in the onset of irreversible shock.

Chapter VII

THE VASOMOTOR MECHANISMS

UNDER the subject of the vasomotor mechanisms may be included all influences, both nervous and chemical, that produce changes in the caliber of the blood vessels. The functions of the vasomotor mechanisms are (1) so to regulate the size of the blood vessels (and thus the resistance to blood flow and the capacity of the vascular system) that there is maintained an arterial pressure sufficiently high to insure an adequate supply of blood to all capillaries, especially those in regions of paramount importance like the brain and heart; and (2) to make such alterations in the distribution of the blood as may be demanded by the varying activities of individual organs.

The subject of the vasomotor mechanisms will be treated from the standpoint of (1) the control of the arterioles, (2) the control of the capillaries, and (3) the control of the venules and veins.

The nervous control of the blood vessels is the subject of a comprehensive review by McDowall.

METHODS OF DETECTING VASOMOTOR ACTION

An important method of detecting vasomotor action is to determine the changes in volume undergone by the organ being studied. An increase in volume usually means vasodilatation in the organ, whereas a decrease usually indicates vasoconstriction. However, such is not always the case, for changes in the volume of an organ may be merely passive owing to alterations of general arterial pressure. Therefore careful control is necessary before such results can be interpreted fully.

Studies of volume changes in organs are usually made with a plethysmograph. This is essentially a rigid chamber for inclosing the organ without disturbing its blood supply. The interior of the plethysmograph communicates through rubber tubing with a recorder. Most plethysmographs use air transmission. Any increase in the volume of the inclosed organ displaces some air from the plethysmograph into the recording system, and the recording lever rises, whereas a decrease in volume causes air to flow from the recording system into the plethysmograph and the lever falls. In this way a graphic record of volume changes can be obtained. Optical records, instead of mechanical records, of the volume changes may be made. Special kinds of plethysmographs have been devised for the various organs.

Color changes, where they can be detected, temperature changes, and the rate of venous flow from organs are other means of detecting vasomotor action. If cardiac output remains constant and vasomotor changes are excluded in other organs, arterial flow, as measured, for example, by the thermostromuhr (p. 145), may be used to signal vasomotor action.

THE NERVOUS CONTROL OF THE ARTERIOLES

The existence of nerves controlling the arterioles has long been recognized. They are the classical vasomotor nerves. They could be designated as arteriomotor nerves.

Vasoconstrictor Nerves. The vasomotor nerves, efferent in nature, are of two kinds, vasoconstrictors and vasodilators. A vasoconstrictor nerve is one which, when stimulated, causes constriction of the arterioles in the part supplied. The following experiment may be cited as illustrative of vasoconstriction.

If the cervical sympathetic nerve in the rabbit is divided, there occurs in a short time a homolateral dilatation of the arteries in the region of the head. This is especially noticeable in the arteries of the ear. These vessels are now widely dilated, the ear has a flushed appearance, and its temperature is elevated. If the cephalic end of the cut nerve is stimulated, the arteries contract again, and the ear becomes pale and cold. Similar events occur in the submaxillary gland when the cervical sympathetic nerve is cut and its cephalic end stimulated. Evidently this nerve supplies constrictor fibers to the arterioles of certain parts of the head. When the nerve is transected the constrictor influence is removed, the arterioles dilate, and the blood flow through the part is increased. When the nerve is stimulated the arterioles contract, and the blood flow is decreased. Another conclusion that may be drawn from this experiment is that the vasoconstrictor nerves and the arterioles which they supply are normally in a state of tonus, which is abolished when the nerves are cut; hence the vasodilatation. Tonus of the arterioles refers to a condition whereby their muscular coat is kept in a state of partial contraction, which is of varying intensity and is due largely to the continuous passage of nerve impulses to them by way of the vasoconstrictor nerves. However, it is well known that tonus of the blood vessels may be due to humoral stimuli as well as nervous, for tonus that has been abolished by section of a vasoconstrictor nerve will reappear after a time, as indicated by a return of the blood pressure to normal. In fact, after removal of the entire sympathetic chain—and hence the abolition of practically all the constrictor pathways—the blood pressure will return to normal. It is believed that increased capillary tonus is also a factor in the restoration of the blood pressure. Possible humoral agents concerned in the restoration of vascular tone are adrenaline and angiotonin.

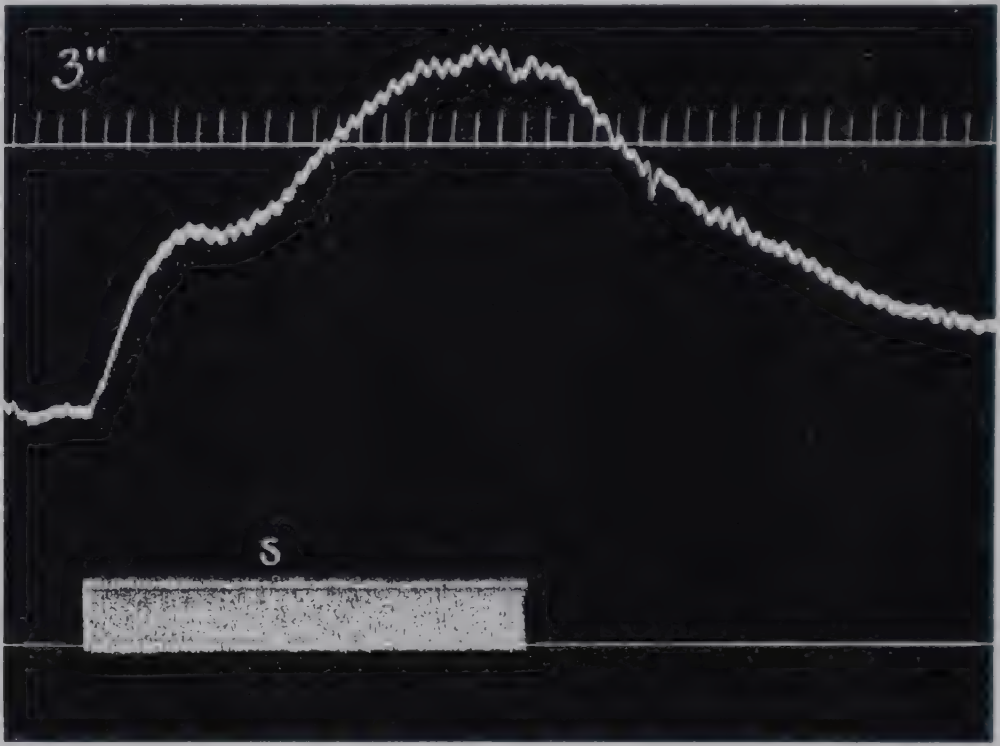

Fig. 56.—Effect of stimulation of the peripheral end of a splanchnic nerve on blood pressure (pig). The signal (s) indicates the duration of the stimulus.

The vasodilatation following cutting of the cervical sympathetic and the vasoconstriction following stimulation of its cephalic end, in the experiment just mentioned, do not involve a sufficiently large area of the total peripheral resistance to cause any general alteration in arterial pressure. To show the influence of the vasoconstrictor nerves on general blood pressure, the splanchnic nerves may be cut on both sides. These nerves supply vasoconstrictor fibers to the abdominal and pelvic viscera (splanchnic area), and when they are cut there is a marked fall in the mean arterial pressure throughout the body. This is due to a decreased peripheral resistance (especially in the arterioles) and to an increased capacity of the circulation (especially in the capillaries). If a splanchnic nerve is now stimulated, the blood pressure returns to normal or above, and remains high as long as the stimulus is maintained (Fig. 56). At the same time the volume of the viscera, which has increased because of cutting the nerves, returns to normal or even less than normal. From this experiment it may be concluded that the vasoconstrictor nerves play a predominant part, particularly in the splanchnic area, in the maintenance of general arterial pressure.

Origin and Distribution of the Vasoconstrictor Nerve Fibers. It has been shown that most (if not all) of the vasoconstrictor fibers emanate from the central nervous system as preganglionic fibers in the white rami communicantes of the sympathetic system. The white rami leave the ventral roots of the spinal nerves at every spinal segment from the first thoracic to the fourth lumbar, inclusive (dog). Every white ramus contains preganglionic vasoconstrictor fibers, which upon entering the neighboring sympathetic chain pass up or down, depending on their destination. Each fiber finally terminates synaptically around a nerve cell in a lateral (vertebral) sympathetic ganglion, or leaves the sympathetic chain and terminates in a similar way in a collateral (prevertebral) sympathetic ganglion. From the ganglionic nerve cell a postganglionic fiber arises and passes to its destination.

The preganglionic vasoconstrictor fibers for the *fore limbs* are given off from the fourth to ninth thoracic ventral roots; those for the *hind limbs,* from the eleventh thoracic to the third lumbar, inclusive. The synaptic junctions of the fore-limb fibers are situated in the stellate ganglion; those of the hind-limb fibers, in the last two lumbar and first sacral sympathetic ganglia.

The preganglionic vasoconstrictor fibers to the *head and neck* arise from the first to fourth thoracic ventral roots and pass up the cervical sympathetic nerve as preganglionic fibers to the anterior cervical ganglion, where they terminate. From nerve cells in this ganglion postganglionic fibers arise and run to their destination via the outer coat of the blood vessels.

The preganglionic vasoconstrictor fibers to the *abdominal and pelvic viscera* arise from the third thoracic to the third lumbar ventral roots, and enter the neighboring sympathetic chain. The thoracic fibers leave it by the greater splanchnic nerves, the lumbar fibers by the lesser splanchnics. They effect synaptic junction in the prevertebral sympathetic ganglia (celiac, anterior mesenteric, posterior mesenteric), from which postganglionic fibers arise and pass along the blood vessels to the arterioles of the abdominal and pelvic viscera.

The existence of vasoconstrictor nerves to the *lungs* was for a long time questioned. It is now pretty generally agreed that the lungs receive vasoconstrictor fibers, the main evidence being based on the fact that adrenaline undoubtedly constricts the arteries of the lungs. It is usually believed, however, that the vasoconstrictor mechanism in the lungs is not highly developed (Dixon and Hoyle, Wiggers). The fibers arise mainly from the third, fourth, and fifth thoracic ventral roots.

As regards the *heart,* the subject of the distribution of vasoconstrictor nerves is not definitely settled. The blood flow through the coronary system is dependent more upon the aortic blood pressure and the activity of the heart than upon nervous control of the local vessels. Bayliss was of the opinion that vasomotor nerves are absent. Wiggers (1923), on the other hand, evaluated the evidence as in favor of the existence of vasoconstrictor fibers but said that the height of blood pressure usually overbalances any active vasomotor changes. Jochim and co-workers have recently studied the innervation of the coronary arteries in the dog. They reached the following conclusions: The sympathetic system supplies both vasoconstrictor (adrenergic) and vasodilator (adrenergic) fibers to the coronary vessels by way of the stellate ganglia. The tonic action of the sympathetic nerves to the coronary vessels is mainly vasoconstriction. The vagi carry only vasodilator (cholinergic) fibers to the coronary vessels. They are in a state of tonus. Jochim and co-workers believe, however, that the effects of the coronary vasomotor nerves are small in the intact animal.

The *cerebral circulation* is dependent mainly upon general blood pressure. However, modern work (Wolff; Cobb and Lennox) shows unmistakably that the cerebral blood vessels receive both vasoconstrictor and vasodilator fibers and that these play a part in regulating cerebral blood flow.

Vasoconstrictor nerves to *skeletal muscles* have been demonstrated.

Vasodilator Nerves. A vasodilator nerve is one whose stimulation causes a dilatation of the arterioles in the part supplied, owing to relaxation of their muscular coats. It is probable that chemical substances released at the nerve terminations cause a decrease in the tonus of the arterioles. The following experiment on the submaxillary gland may be cited as an example of vasodilatation. When the chorda tympani nerve is cut, nothing in particular happens; but when the end in connection with the submaxillary gland is stimulated, vasodilatation occurs, which may be so pronounced that the venous blood leaving the gland has an arterial color and may pulsate. The general blood pressure remains unaffected. From this experiment it may be concluded (1) that the chorda tympani contains fibers whose function is to dilate the arterioles of the submaxillary gland, thus increasing the volume of blood flowing through it, and (2) that these fibers are not in a state of tonus, because when they are transected no constriction of the vessels takes place, that is, no tonic dilator influence has been removed.

Origin and Distribution of the Vasodilator Nerves. The arrangement of the vasodilator nerve fibers is different from that of the vasoconstrictors. Irregularity characterizes the arrangement of the former, whereas uniformity characterizes the arrangement of the latter. In general, it may be said that as regards their anatomical arrangement vasodilator fibers can be grouped under three headings: (1) those distributed through cranial and sacral autonomic nerves; (2) those that leave the central nervous system in the dorsal roots of the spinal nerves; and (3) those that run in the sympathetic system.

1. The best example of a cranial autonomic vasodilator nerve is the chorda tympani, stimulation of which, as has been stated, causes dilatation of the arterioles in the submaxillary gland. Vasodilator fibers are also found in the nerves supplying the other salivary glands and possibly the tongue and certain other head structures. Similar fibers are given off from the spinal cord in the ventral roots of the second and third sacral nerves. They run in the pelvic autonomic nerves (nervi erigentes) to the blood vessels of the external genital organs. Stimulation of these fibers causes vasodilatation in these organs, and in the male the vascular engorgement of the penis results in erection. In all instances where vasodilator fibers have cranial or sacral autonomic distribution, their peripheral synaptic junctions are believed to be located close to or within the organ supplied.

2. Vasodilator fibers in the dorsal roots of some of the spinal nerves have been demonstrated by Bayliss and others. When the dorsal roots of the limb plexuses are stimulated, vasodilatation, mainly in the skin but to some extent in the muscles of the limbs, is obtained. The same thing happens when the mixed nerves to these parts are stimulated. The fibers that bring about this result are believed to be identical with the ordinary sensory fibers of the limbs. One of the fundamental conceptions regarding the conduction of the nerve impulse is that it is in one direction only. Vasodilatation brought about by afferent nerves would, if it actually occurs under normal conditions, constitute an important exception to the general rule. A possible explanation of this peculiarity (Bayliss) is that the dorsal root fibers divide near their peripheral ends, one branch ending in a receptor in the skin or muscle, and the other in the wall of a nearby arteriole. Therefore an impulse traveling along the fiber in the direction opposite to the usual would cause vasodilatation only. Such an impulse, because of its direction of travel, is said to be *antidromic*.

Of interest at this time is the fact that the application of an irritant to the skin causes vasodilatation, which is abolished when the cutaneous receptors are paralyzed by cocaine. That this effect is not due to a true reflex is indicated by the observation that it still takes place when the nerves have been completely separated from the spinal cord. That a sensory nerve fiber and a branch from this fiber to the blood vessel are involved in this reaction is indicated by the fact that when the nerve fibers are caused to degenerate (by separating them from their cells of origin in the dorsal root ganglia), vasodilatation does not occur when the irritant is applied to the skin (Bruce). The accompanying diagram (Fig. 57) shows a nervous arrangement that might be involved in this "axon reflex."

To what extent normal vasodilatation in the skin and muscles may be brought about by antidromic impulses and to what extent they may be brought about by a peripheral mechanism such as that just described cannot be stated at present. It is possible that both mechanisms can operate under normal conditions. Assuming that reflex antidromic vasodilatation is a normal occurrence, it is not clear how the central terminations of the afferent fibers are stimulated to conduct nerve impulses in the opposite direction.

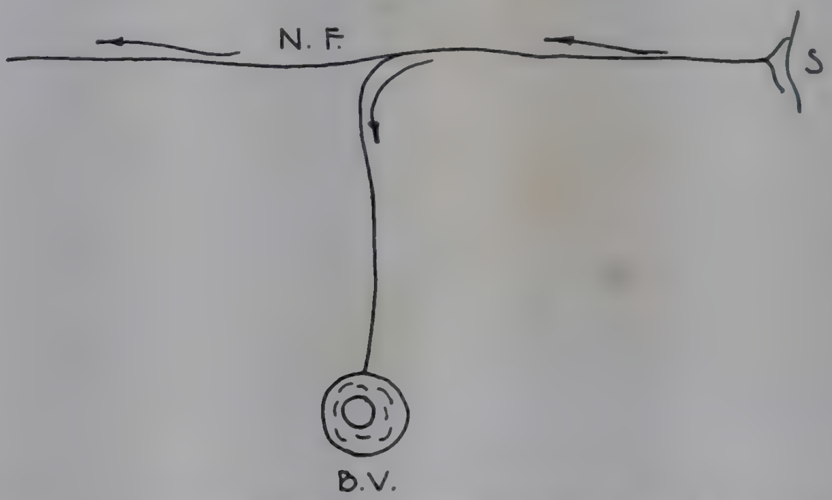

FIG. 57.—Diagram illustrating how local vasodilatation could be brought about as a result of the application of an irritant to the skin. S, skin; B.V., blood vessel; N.F., afferent (sensory) nerve fiber, part of which supplies the skin and part a blood vessel. The arrows indicate the direction of passage of the nerve impulse when the skin is irritated.

3. Although Bayliss was of the opinion that practically all experiments showing vasodilatation upon stimulation of sympathetic nerves could be explained by the action of metabolites or by antidromic effects, more recent work points to the presence of true vasodilator fibers in the sympathetic system. The subject of sympathetic vasodilator fibers has been reviewed by Burn. The dog and hare—animals resistant to fatigue—have many sympathetic vasodilator fibers to the muscles. They are cholinergic, at least in the dog. The cat has a few sympathetic vasodilator fibers to the muscles, whereas the rabbit and monkeys have none. The dog has some sympathetic vasodilator fibers to the intestine. They are believed to be adrenergic. The coronary

arteries of the dog receive sympathetic vasodilator fibers. They are adrenergic (p. 178). Sympathetic vasodilator fibers to the skin have been demonstrated, but they are less important than sympathetic vasoconstrictor fibers to the skin.

Vasomotor Centers. It has already been stated that vasoconstrictor fibers leave the spinal cord in a definite region—the outflow that forms the sympathetic system; whereas the vasodilator fibers are more irregular in origin. It has been stated further that the vasoconstrictor fibers are in a state of tonus, whereas the vasodilators are not. The latter are active only during the functional activity of the parts supplied. The question now to be discussed deals with the final central origins of the vasoconstrictor and vasodilator paths, the vasomotor centers.

Vasoconstrictor Center. Section of the brain-stem above the middle of the pons is usually without effect on blood pressure, except perhaps in birds (pigeons—Rogers), whereas successive slicings beginning at the middle of the pons and continued downward cause a progressive drop in pressure until the upper part of the spinal cord is reached. Thence further slicing is without effect. This experiment is interpreted to mean that there is a vasoconstrictor center with upper and lower limits approximately as indicated, and that the center constantly sends tonic constrictor impulses to the arterioles. Ranson states that the center is "located in the medulla oblongata at about the level of the motor nucleus of the facial nerve." Other evidence places the center in or near the vestibular nuclei. It is a bilateral center. The vasomotor paths descend in the lateral funiculus of the spinal cord.

The tonus of the vasoconstrictor center (and therefore of the peripheral arterioles) is due to at least two sets of influences: (1) the action of the blood gases, mainly the carbon dioxide, and also perhaps the increased hydrogen ion concentration that an increased amount of carbon dioxide induces; and (2) the continuous stimulation of the center by afferent impulses. The cause of the tonus of the center is thus in part humoral and in part reflex. Both of these factors are subject to variation. By virtue of this tonus the center sends never-ending though variable trains of impulses to the arterioles, maintaining them in a state of partial contraction.

Subsidiary vasoconstrictor centers exist in the spinal cord. These are normally under the influence of the vasoconstrictor center in the medulla. That this is true is indicated by the fact that section of the cord in the cervical region results in a sudden and distinct fall of blood pressure; the blood vessels are thus cut off from the medullary center and therefore dilate. However, after some time the blood pressure rises. The principal reason for this is the acquisition of tonic activity by the spinal centers. If the splanchnic nerves are now transected the blood pressure falls again. This fall is partially recovered from because of the development of a peripheral vascular tonus.

Vasodilator Center. The present evidence points to the existence of a medullary vasodilator center comparable to the vasoconstrictor center. It is not regarded, however, as being tonically active. Two lines of evidence in favor of the existence of a vasodilator center in the medulla may be summarized as follows (Ranson).

1. Stimulation of the aortic nerve causes a fall of blood pressure not only by decreasing the tone of the vasoconstrictor center but also by causing an active vasodilatation in widely separated parts of the body. Such diffuse dilatation can be satisfactorily explained only by assuming the existence of a supreme vasodilator center, which is called into action by the stimulation.

2. Stimulation of a certain point in the floor of the fourth ventricle causes vasodilatation and a fall of blood pressure. Stimulation of no other point causes vasodilatation.

The vasodilator center, like the vasoconstrictor, is activated reflexly and also probably by changes in the composition of the blood. The vasodilator center is involved in the general vasodilator reflexes, that is, those vasodilator reflexes that cause a fall in blood pressure. There is an accompanying reciprocal inhibition of the vasoconstrictor center. Some vasodilator reflexes are local, that is, the resulting vasodilatation occurs only in the region from which the stimulus arises, and no fall of general blood pressure is evident.

Vasomotor Reflexes. It was stated above that the vasomotor centers are susceptible to reflex control. This is one of the important ways of varying the degree of their activity.

Pressor Reflexes. Most afferent nerves contain fibers whose stimulation causes a reflex rise in blood pressure. Such fibers are designated as *pressor fibers,* and the rise in arterial pressure that their stimulation brings about (Fig. 58) is called a *pressor reflex.* Pressor fibers are more susceptible to strong stimulation than to weak. The question arises whether pressor reflexes take place through the vasoconstrictor center or the vasodilator center or both. That the tonus of the vasoconstrictor center may be increased reflexly, with a resulting elevation of arterial pressure, is evident from numerous experiments by many workers. That the vasodilator center is ordinarily not involved (that is, not inhibited) in a reflex rise of blood pressure is indicated by the fact that the center is usually not in a state of tonus. Under certain experimental conditions, however, vasoconstriction and a rise of blood pressure may be brought about by inhibition of vasodilator tonus (Bayliss).

Nerve impulses which give rise to pressor reflexes ascend the spinal cord in the dorsolateral fasciculus (Fig. 135, p. 595). Pressor fibers may be identical with certain types of pain fibers.

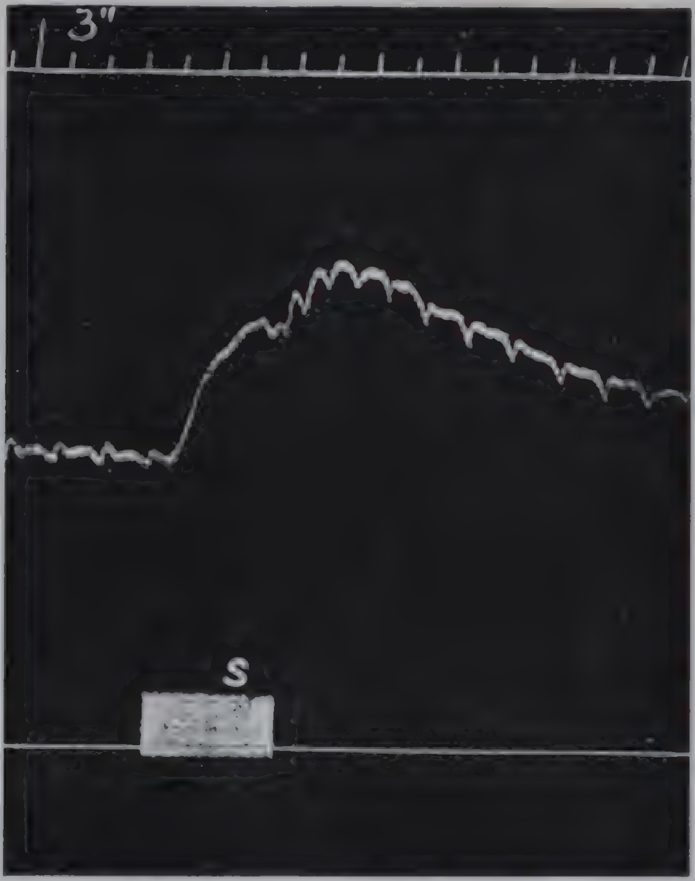

FIG. 58.—Effect of stimulation of central end of vagus nerve on blood pressure—pressor reflex (pig). The signal (s) indicates the duration of the stimulus.

Depressor Reflexes. Under certain conditions of stimulation of the central end of an ordinary nerve, a reflex fall in arterial pressure may be obtained (Fig. 59). Such a reflex is designated as a *depressor reflex.* Some of the conditions are (1) weak stimulation of the nerve; (2) stimulation of the nerve cooled to 4 or 5 degrees C.; (3) mechanical stimulation of afferent nerves in muscles. It may be concluded, therefore, that *depressor fibers* are contained in many of the nerves of the body. They connect with interneurons in the spinal cord which reach the medulla. The question arises whether depressor reflexes are due to a decrease in the tonus of the vasoconstrictor center or to an excitation of the vasodilator center or both. It would be supposed that both effects probably take place, and experimental work indicates that they do.

A depressor nerve of great importance is the aortic nerve (p. 125). This nerve is composed chiefly of afferent fibers with terminations in the wall of the aorta. It runs to the medulla oblongata as a separate nerve in the rabbit and opossum but is incorporated with the vagus in most animals. Stimulation of its central end usually causes a fall in blood pressure (Fig. 60) due to reflex vasodilatation in all parts of the body supplied with vasomotor nerves. Reflex slowing of the heart also occurs. It has been shown that this depressor reflex is due mainly to an inhibition of the tone of the vasoconstrictor center but in some degree to a stimulation of the vasodilator center. The aortic nerve protects the heart against too high a rise in arterial pressure. At every beat of the heart the blood pressure rises, and pressure receptors in the aorta are mechanically stimulated as a result of the stretching of its wall; whereupon impulses pass to the chief vasoconstrictor and vasodilator centers in the medulla, inhibiting the one and stimulating the other. In this way the peripheral resistance and the aortic blood

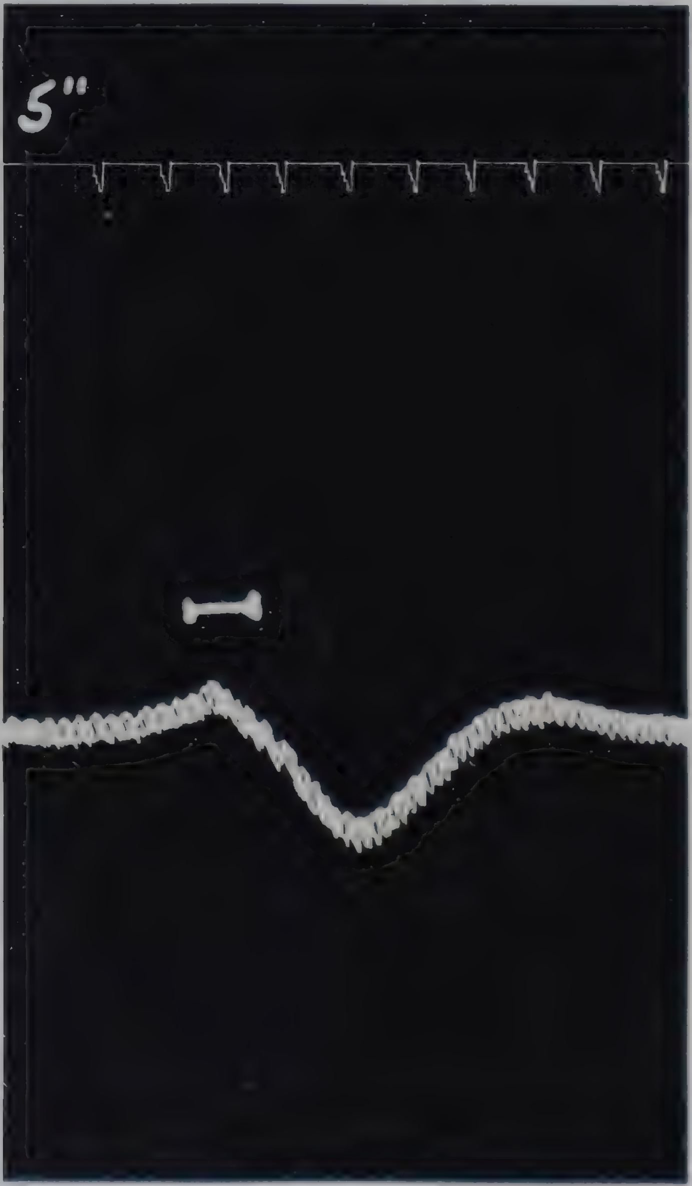

Fig. 59.—Effect of weak stimulation of central end of sciatic nerve on blood pressure—depressor reflex (dog). I—I indicates the duration of the stimulus.

pressure are co-ordinated. In close functional relation with the aortic nerve are afferent nerve fibers with receptors in the carotid sinus. These fibers form the sinus nerve (p. 126). Stimulation of pressure receptors in the wall of the carotid sinus causes a reflex fall of blood pressure through the vasomotor centers. Cardiac slowing also often occurs. The mechanism is tonic in action, and the number of nerve impulses passing from the receptors in the sinus to the central nervous system depends upon the intrasinusal pressure (Fig. 61).

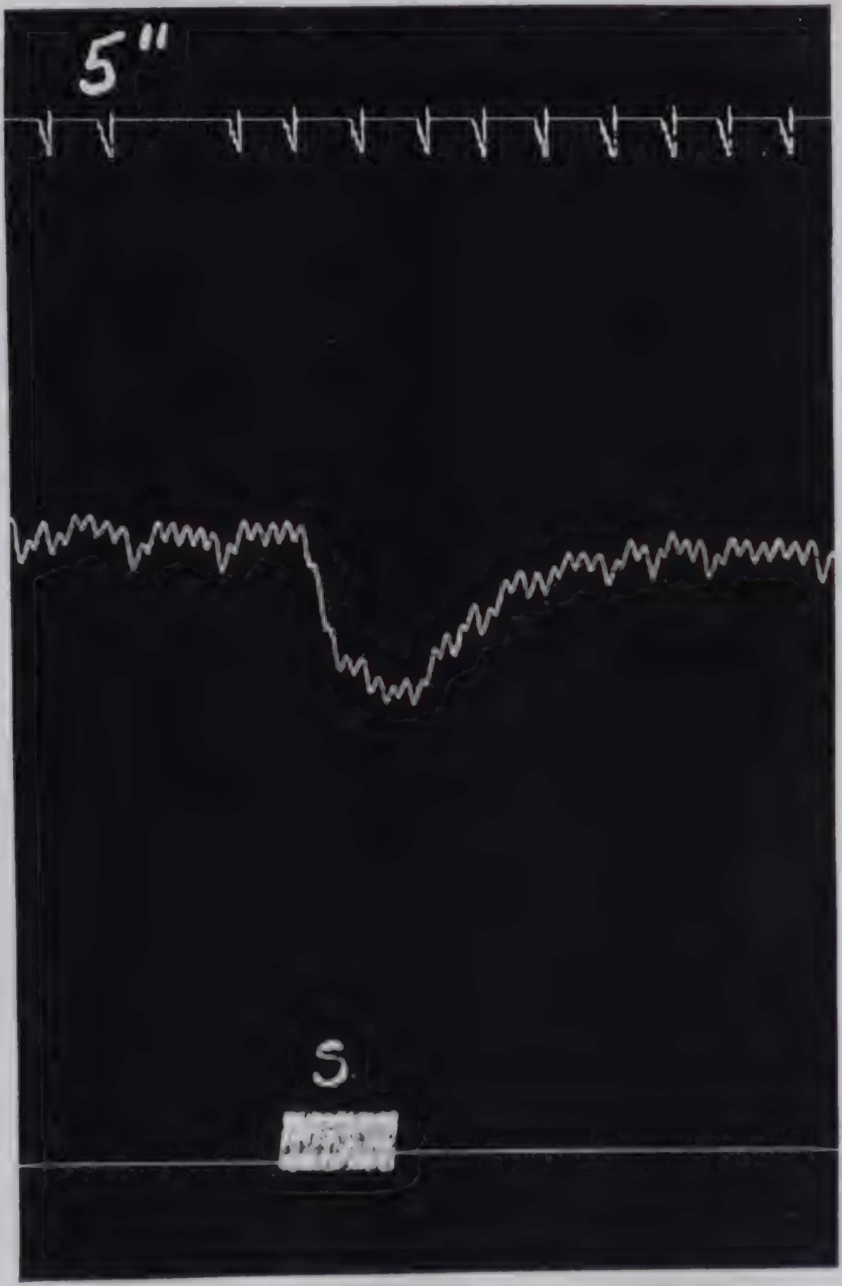

Fig. 60.—Effect of stimulation of the central end of the aortic nerve on blood pressure (rabbit). The signal (s) indicates the time and duration of the stimulus.

Other Effects on the Vasomotor Centers. There is a great deal of evidence that the *hypothalamus* can influence the activity of the heart and blood vessels (Bronk, 1940). However, the hypothalamus is not essential to cardiovascular regulation. Centers in the medulla suffice. This is indicated by the fact that cardiovascular regulation is satisfactory in the decerebrate animal. The hypothalamus exerts its effect on the cardiovascular apparatus through the medullary centers. Hypothalamic control of the cardiovascular centers in the medulla is probably concerned primarily with heat regulation and emotional states.

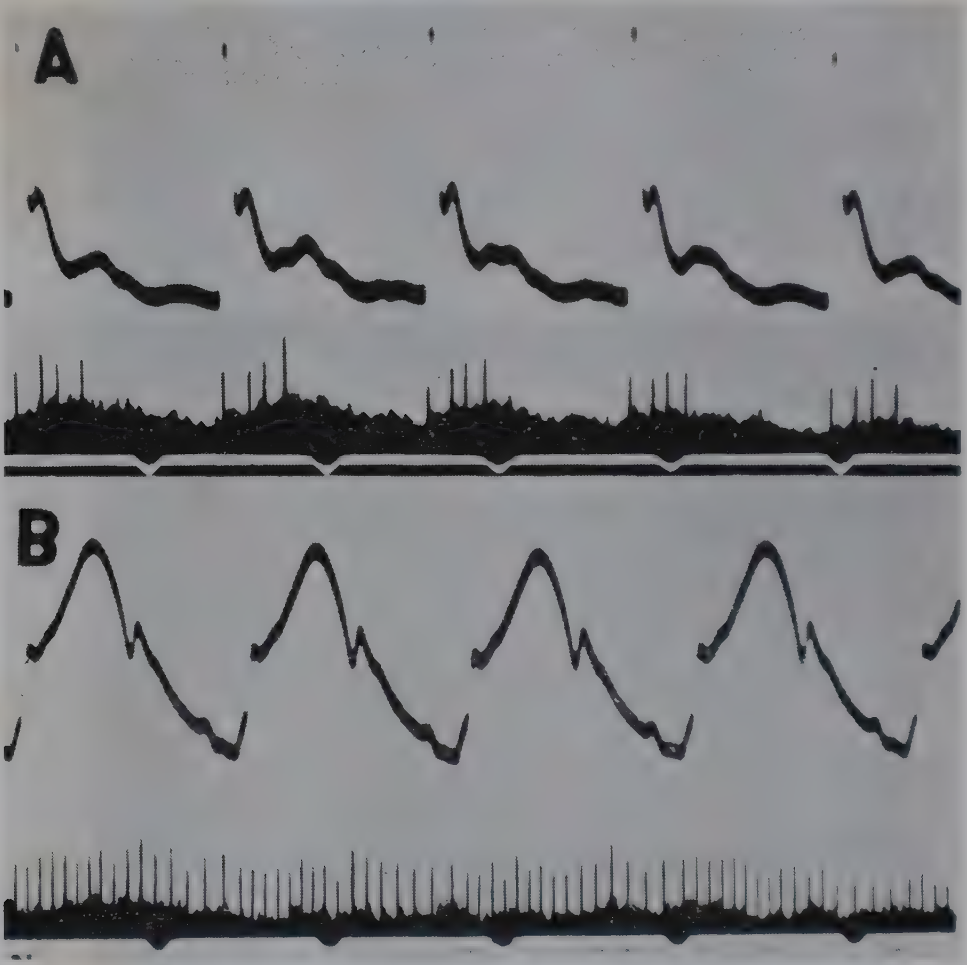

Fig. 61.—Curves of the pressure pulse and (under them) records of afferent impulses from a single pressure receptor in the carotid sinus. Note the increased frequency of discharge in B. This was caused by an injection of adrenaline which elevated the mean arterial pressure from 55 mm. Hg in A to 135 mm. in B. Time, 1/5 sec. (Bronk and Stella; from Bronk, *Research Publications of the Association for Research in Nervous and Mental Disease,* 1940, 20.)

The vasomotor mechanisms may be brought under the control of the *cerebral cortex.* Electrical stimulation of the motor and premotor areas of the cerebral cortex brings about vasomotor changes in various parts of the body. It is suggested that in this way the increased blood supply to muscles brought into action by the cerebral cortex may be anticipated (Green and Hoff).

Stimuli from the *skin* (heat, cold, pain) may cause vasomotor changes. Heat usually causes a depressor effect, cold a pressor. Mild pain may cause the blood pressure to rise or fall. Severe pain causes a fall.

Chemoreceptors (chemoceptors) in the *aortic* and *carotid bodies* (p. 127) are of some importance in the regulation of the vasomotor and cardio-inhibitory centers. The following factors have been shown to be stimuli for the chemoreceptors and thus to increase the activity of the vasomotor and cardio-inhibitory centers (Schmidt and Comroe): anoxemia, carbon dioxide excess, and a decrease of *p*H. The chemoreceptors are responsible for the hypertension that occurs in anoxia, but there is little evidence that they are essential to the normal regulation of blood pressure. The chemoreceptors in relation to respiration are discussed elsewhere (p. 243).

Receptors in the *mesentery* (Pacinian corpuscles) discharge nerve impulses that are probably concerned in the reflex regulation of the circulation. The impulses were detected by electrical means in the splanchnic and mesenteric nerves. The effective stimulus to the receptors appears to be distention of the mesenteric blood vessels (Gammon and Bronk).

THE CHEMICAL CONTROL OF THE ARTERIOLES

What was said above about the control of the arterioles referred to their control through the vasomotor (arteriomotor) nerves. Probably in most instances the nerves are excited reflexly by mechanical or thermal stimulation of receptors. In some instances, however, the nerves are excited reflexly by the action of chemical substances on chemoreceptors and in other instances by the action of chemical substances on the vasomotor centers themselves.

It now remains to consider briefly the action of chemical substances on the arterioles themselves.

Metabolites. This term refers to products formed during metabolism. Experimental evidence shows that at least two of these, lactic acid and carbon dioxide, are vasodilators. By reason of this action they help to bring about an increased blood supply to an organ during its functional activity. Vasodilatation by metabolites is doubtless supplemented by reflex vasodilatation. According to Bayliss the acid products of metabolism are vasodilators by virtue of the hydrogen ions to which they give rise. Alkalis produce the opposite effect; they are vasoconstrictors.

Adrenaline. This is a hormone produced by the medulla of the adrenal glands. Its action is that of a stimulant to sympathetic nerve endings; hence it is in most locations a vasoconstrictor substance, in others a vasodilator. It is very active, one part in 250 million causing vasoconstriction. Smaller doses may cause vasodilatation.

Pituitary Extract. Extracts of the posterior lobe of the pituitary (pitressin, vasopressin) stimulate the musculature in the walls of the blood vessels. This is another example of a vasoconstrictor substance produced by an endocrine organ.

Other Substances. *Histamine* is a decarboxylation product of the amino acid histidine. It is widely present in an inactive form in the animal body. Histamine has a powerful vasodilator effect. It has been suggested that it may be released from damaged tissue in quantity sufficient to account for the vasodilatation and fall in blood pressure seen in traumatic shock.

Adenylic acid occurs in muscle as a component of adenosine triphosphate. During muscular contraction this substance breaks down into adenylic acid and phosphoric acid. Injected intravenously adenylic acid has a vasodilator and cardio-inhibitory effect. The suggestion has been made that adenylic acid is normally concerned in the vasodilatation that accompanies muscular contraction, and that following tissue damage it may enter the blood stream in amounts large enough to cause a fall of blood pressure.

Angiotonin is a factor in experimental hypertension and is probably concerned in essential hypertension in man (p. 163). To what extent, if at all, it participates in the regulation of normal arteriolar tone is unknown.

THE CONTROL OF THE CAPILLARIES

Until comparatively recently it was customary in discussions dealing with the regulation of the blood vessels to assume that the capillaries are passive tubes so far as any changes in their caliber are concerned. It was well known from microscopic studies that the capillaries undergo variations in size, but these changes were thought to be merely passive because of pressure changes on their interior. Changes in the caliber of the arterioles were thought to be adequate to explain vasomotor control of the circulation. Later work (Krogh; Hooker, 1921) seems to show that the capillaries, as well as the arterioles, undergo active changes in caliber and that any consideration of the vasomotor mechanisms that ignores these changes is incomplete.

Anatomically a capillary is usually stated to be a bare endothelial tube supplied with nerve fibers. However, Rouget, in 1873, and subsequent investigators, including in late years Krogh and his co-workers, have described what appear to be specialized muscle cells surrounding the capillaries, or more exactly the precapillaries, at intervals but not forming a continuous layer. These Rouget cells, as they are called, have been shown to possess contractile power and have been described in mammals (mouse, cat). It is doubted that they are widely present in higher mammals. Arteriolo-venular bridges (p. 138) have widely separated muscle cells in their walls.

Active changes in the caliber of capillaries are described as being due to two possible causes: swelling of the endothelial cells and contraction of muscle cells. Irrespective of how changes in capillary diameter are brought about, there is rather general agreement that active changes do occur and are of significance in the normal regulation of blood flow through the capillaries (Hoerr).

Several kinds of direct stimuli (mechanical, thermal, electrical), many chemical substances (carbon dioxide, nicotine, adrenaline, histamine, urethane, weak acids), and stimulation of certain nerves have been shown to cause motor effects on the capillaries. Hooker (1921) generalized these facts by saying that chemical factors appear to cause dilatation of the capillaries and venules, whereas nerve stimulation causes constriction. He expressed the opinion that the chemical regulation is local, causing changes in the blood supply in accordance with the varying needs of the different tissues. The nervous control, on the other hand, appears to maintain a capillary tonus, which can be relaxed by chemical factors (metabolites, etc.). The field of capillary motility is by no means settled. Considerable differences of opinion still exist among competent workers. Further researches will be required to clarify the conflicting ideas.

THE CONTROL OF VENULES AND VEINS

From the anatomical standpoint a venule consists of an endothelial tube and a layer of connective tissue overlying it. Venules, like capillaries, receive nerve fibers. In investigations on the motility of capillaries it has been found that venules behave in a similar way (Hooker, 1921). Hence they must be added to the list of vessels under nervous and chemical control.

Concerning the motor innervation of large veins not a great deal is known. It has been shown by a number of workers that veins receive sympathetic innervation, this conclusion being based mainly on the fact that adrenaline constricts many veins (Franklin). The branches of the portal vein in the liver really act as arterioles, and they receive vasoconstrictor fibers from the splanchnic nerves. The veins of the hind limb, in the cat and dog, receive sympathetic vasoconstrictor fibers that leave the spinal cord in the ventral roots of the second to the fourth lumbar nerves. Experimental work indicates that these *venomotor fibers* are of assistance in maintaining venous tonus, which, it might be supposed, is for the purpose of limiting the venous bed and facilitating the return of blood to the heart.

SOME VASOMOTOR RESPONSES IN THE PIG AND SHEEP

Very little work has been done on vasomotor action in farm animals. Dukes and Schwarte reported some acute experiments in the *pig*. Ligation of both carotid arteries caused little or no effect on blood pressure. Asphyxia caused the blood pressure to rise sharply. Stimulation of the central end of the vagus nerve caused a rise of blood pressure more often than a fall. Negative effects were more common with the left nerve. No experimental evidence of the existence of a separate aortic nerve was found. In the pig the cervical sympathetic nerve on both sides is separate from the vagus. Stimulation of the central end of the sciatic nerve usually gave a pressor effect, although negative results were not uncommon; a fall of blood pressure was seldom obtained. Stimulation of the peripheral end of the splanchnic nerve caused a rise of blood pressure, in some instances as great as 100 per cent. Stimulation of the central end of the splanchnic nerve caused a rise of blood pressure. As judged by the fall in blood pressure following spinal transection, the vasoconstrictor center of the pig possesses appreciable tone.

Some observations on vasomotor responses in *sheep* have been made by Rangsit. The usual effect on blood pressure of stimulation of the central end of the vagus nerve was a rise. Stimulation of the peripheral end of the splanchnic nerve caused a distinct rise of blood pressure. The primary effect of histamine on blood pressure was to cause a fall. In some instances the fall was followed by a rise.

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PART III

Respiration

Chapter VIII

THE MECHANICS OF RESPIRATION

RESPIRATION is the gaseous exchange between an organism and its environment. All the energy displayed by the animal body comes in the long run from the oxidation of complex carbon-containing molecules, and one of the end-products of this oxidation is carbon dioxide. Therefore a constant supply of oxygen and the elimination of carbon dioxide are necessary for all animal existence. In the simplest forms of life respiration takes place directly between the organism and its environment, whereas in the higher animals a system of respiratory organs is present, the purpose of which is to bring the air or oxygen-containing water into relationship with the circulating blood, by which the oxygen is transported to the tissues and the carbon dioxide carried to the lungs or gills for elimination. In higher animals external respiration and internal or tissue respiration are therefore differentiated. By the former is meant the gaseous exchange between the environment and the blood in the pulmonary capillaries; by the latter, the gaseous exchange between the blood in the systemic capillaries and the tissues as well as the complicated processes of the physiological oxidations in the cells. In each type of respiration oxygen is absorbed and carbon dioxide is given off. A study of respiration must therefore account for the means whereby oxygen is supplied to and utilized by the organism and carbon dioxide is removed from it.

THE RESPIRATORY APPARATUS

The mammalian respiratory apparatus consists of the lungs and the air passages leading to them, the thorax and the pleural sacs contained therein, the muscles which increase or decrease the size of the thorax, and the afferent and efferent nerves connected with these structures.

The *air passages* are the nasal cavity, pharynx, larynx, trachea, and bronchi. All of these are well constructed to serve the purpose of a continuous air tube to the lungs. The mucous membrane of the nasal cavity is moist and highly vascular, and contains numerous glands, thus serving to add warmth and moisture to the inspired air. The pharynx is a common passageway for the respiratory and digestive tubes. The larynx is a musculocartilaginous valvular structure serving as the principal organ of phonation and under some circumstances as a regulator of the amount of air entering or leaving the lungs. The vocal cord and the arytenoid cartilage on each side form the boundary of the glottis, which may be so tightly closed by apposition of these structures as completely to block the respiratory passage. The trachea is kept always open by the presence of incomplete rings of cartilage in its wall. Its mucous membrane has numerous mucous glands, and its epithelium is ciliated. The secretion of the glands and the cilia help to prevent the entrance of dust and other foreign matter into the lungs. The bronchi are similar in structure and function to the trachea.

The *lungs* may be regarded as two elastic membranous sacs whose interior, in free communication with the outside air through the respiratory passages, is highly modified and enlarged by the presence of numerous alveoli. These are hemispherical outpouchings from the alveolar sacs. The latter communicate by way of their respective atria with an alveolar duct. The alveolar ducts are direct branches of the respiratory bronchioles; they possess a small amount of muscle in their walls. The respiratory bronchioles are fine divisions formed by a complex branching and rebranching of the two main bronchi after they enter the lungs. Their walls contain no cartilage, but muscular tissue is present. Large bronchioles, however, possess both cartilage and muscle. The bronchiolar musculature is regulated by bronchoconstrictor and bronchodilator fibers. Experiments show that both kinds of fibers reach the bronchioles by the vagi and by the sympathetic nerves. These fibers are the efferent pathways for a variety of reflexes acting on the bronchioles.

The wall of an alveolus is composed of a single layer of respiratory epithelium. Across this layer of cells and the endothelium of the capillaries gaseous exchange between the air in the alveoli and the blood in the numerous adjacent capillaries takes place. The delicate layer of connective tissue supporting the alveoli and capillaries is fenestrated and therefore does not constitute an additional membrane across which diffusion has to take place.

The respiratory bronchioles, alveolar ducts, and atria also possess outpouchings similar to the alveoli just described. These therefore contribute additional surface for gaseous exchange. The total number of alveoli in the lungs of man has been estimated to be some 725,000,000, and the surface they present about 200 square meters,[1] or 100 to 130 times the surface of the body (Reichert). The surface presented by the capillaries of the lungs is estimated to be about 90 square meters.

The lungs are actually much smaller than the thoracic cavity which they occupy. However, they are expanded by the pressure of the atmosphere on their interior so that at all times they completely fill all parts of the chest not otherwise occupied.

The *thoracic cavity* is the body cavity that contains the lungs and mediastinal organs. This cavity has no communication with the outside and is completely separated from the abdominal cavity by the diaphragm. During life the size of the thorax, and therefore the size of the distended and elastic lungs, is constantly undergoing variations brought about by the action of the respiratory muscles.

The *pleurae* are two serous membranes inclosing, on each side, a pleural cavity. They line the thoracic cavity, form the lateral walls of the mediastinum, and are reflected therefrom on the lungs. The cavity is merely a capillary space between the parietal and visceral parts of the pleura. It contains a thin film of fluid, which serves to moisten and lubricate the two pleural layers. In certain pathological conditions (pleurisy, hydrothorax) the amount of fluid may be increased, and the degree of expansion of the lungs therefore correspondingly decreased. The pressure in the pleural cavities is negative. Therefore when a plural cavity is opened, either through the thoracic wall or the lung, air rushes in and the lung collapses.

THE MECHANISM OF INSPIRATION

By an inspiration is meant an enlargement of the thorax and lungs and the accompanying inrush of air. Since the lungs accurately follow all changes in the size of the thorax, any force that increases the size of the thorax must also produce an inspiration. There are two ways of enlarging the thorax and producing an inspiration, namely, by a contraction of the diaphragm and by a forward and outward movement of the ribs.[2]

Contraction of the Diaphragm. The diaphragm, the principal muscle of inspiration, is dome-shaped; the thoracic surface is convex, the abdominal surface concave. Its rim is muscular, its center tendinous, its lumbar part muscular. It is attached to certain ribs, the first four or five lumbar vertebrae, and the xiphoid cartilage. Contraction of the diaphragm lessens its curvature and so increases the longitudinal diameter of the chest; the contracting diaphragm tends to become an inclined plane. The increased length of the thorax results at once in a backward movement of the lungs. The pressure on their interior being somewhat reduced, outside air rushes in, and an inspiration is produced. In addition to the expansion and filling of the lungs, abdominal changes take place during the backward movement of the diaphragm: intra-abdominal pressure is increased throughout, the abdominal organs are displaced backward, the abdominal muscles relax, and the abdominal wall protrudes. Respiration in which movements of the diaphragm are prominent is called diaphragmatic or abdominal respiration.

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[1] Other estimates are 90 and 140 square meters. The body surface of a man of average size is about 1.65 square meters.

[2] In bipeds the ribs are elevated during inspiration.

The motor nerves of the diaphragm are the phrenics, one for each half. Section of a phrenic nerve leads to paralysis of the diaphragm on the same side on which the cut is made. However, the observation has been made on dogs that experimental paralysis of the diaphragm does not seriously interfere with respiration. Dogs "in which the whole of the diaphragm was paralyzed by bilateral phrenic neurectomy ran and played like normal animals and after exercise could not be separated from normal dogs by those who were not acquainted with them" (Lemon). It appears therefore that in dogs, at least, diaphragmatic contraction cannot be regarded as of supreme importance in respiration; the loss of respiratory function of the diaphragm can be completely compensated for by the action of other muscles.

Movements of the Ribs. Each rib has two points of articulation with the vertebral column. The head articulates with facets on the bodies of adjacent vertebrae, and the tubercle with a facet on the transverse process. The chief movement that any rib can undergo is rotation around an axis which passes through the centers of the head and tubercle. In inspiration the movement of the anterior series of ribs is limited; but the movement of the posterior series is considerable, is mainly outward and forward, and results in an increase of the transverse diameter of the thorax. Chauveau states that there is also some increase in the vertical diameter of the chest owing to rib movements displacing the sternum downward. In man the sternum does not have to support so much weight as it does in quadrupeds. Therefore its movements in respiration are greater.

As regards the muscles concerned in the production of these rib movements, it has been shown experimentally that the external intercostals and the intercartilaginous parts of the internal intercostals contract synchronously with the diaphragm and are therefore inspiratory in function (Hough; Schafer and Macdonald). That these muscles are inspiratory in function is further indicated by the work of Bronk and Ferguson, who studied the electrical changes in motor nerve fibers supplying the muscles. The following additional muscles are, on anatomical grounds, usually classed as inspiratory: levatores costarum, serratous dorsalis anterior, latissimus dorsi (except in equines), serratus thoracis (forced inspiration).

Accessory Respiratory Movements. In addition to the inspiratory movements just considered, accessory movements are seen, especially when the respirations become labored. Thus in the rabbit in ordinary breathing, in the horse when the breathing is at all difficult, and in man when it becomes distinctly difficult, elevation of the wings of the nostrils occurs simultaneously with inspiration. In many animals, also, the glottis is further widened during inspiration. These movements serve to reduce the resistance to the inflow of air by widening the passageway.

Roaring. This is a disease of the horse in which there is a severe disturbance of the action of the laryngeal muscles because of paralysis of the recurrent nerve. The left cricoarytenoideus dorsalis muscle is paralyzed, and other muscles on the same side may be involved to a varying extent. Occasionally both sides of the larynx are affected at once, or affection of the left side may be followed later by involvement of the right. Disease of the right side alone is rare (Bemis). Since the recurrent nerve innervates all the intrinsic muscles of the larynx except the cricothyroideus (Sisson), it is difficult to understand why the paralysis should involve the cricoarytenoideus dorsalis (abductor) muscle so completely and the adductors so little. Apparently the innervation of the larynx of the horse requires further study.

The distress in roaring occurs on inspiration. It is caused by the fact that the left arytenoid cartilage, whose muscle is paralyzed, is drawn into the glottis on inspiration. This also opens the ventricle wider.

The left recurrent nerve is closely related to the bronchial and anterior mediastinal lymph nodes. These are often affected in strangles. Extension of the inflammation to the left recurrent nerve may explain why it is more frequently paralyzed in roaring.

Experimental transection of the left recurrent nerve produces the symptoms seen in clinical cases of roaring.

THE MECHANISM OF EXPIRATION

By an expiration is meant a decrease in the size of the thorax and lungs, and the accompanying outflow of air. Following an inspiration, the enlarged thorax *may* return to its resting position by purely passive forces, that is, without muscular effort. The physical factors concerned are the weight and distortion of the ribs, the distortion of the costal cartilages, the elasticity of the distended abdominal wall, and the elasticity of the lungs. Experiments have revealed, however, that passive expiration—at least in dogs—is not the usual condition (Gesell, 1936). Records of the action potentials of the respiratory muscles in quiet breathing showed that although expiration may be entirely passive, yet in the great majority of cases varying degrees of active expiration occur. Labored respirations are known to be accompanied by definitely active expirations, the return of the thorax to the resting position being hastened. Very active expirations are seen also in coughing, talking, laughing, barking, and lowing. Expiratory muscles may be divided into two groups:

1. Those muscles whose contraction exerts pressure on the abdominal viscera and so on the posterior face of the diaphragm, driving it forward into its resting, expiratory position. Such are the abdominal muscles, and the following ones are capable of this action: obliquus abdominis externus, obliquus abdominis internus, rectus abdominis, and transversus abdominis.

2. Those muscles whose contraction hastens the return of the ribs to their ordinary expiratory position. The internal intercostals (interosseous portion) and the tranversus thoracis have been shown by experimental means to be expiratory. Muscles whose attachments suggest that they are, or may be, expiratory are the serratus dorsalis posterior, longissimus costarum, and longissimus dorsi.

EUPNEA, DYSPNEA, HYPERPNEA, POLYPNEA, APNEA

Eupnea is the state of ordinary quiet breathing. The animal is unaware of the effort required to produce the thoracic movements.

Dyspnea is a condition of labored breathing. There are many degrees of dyspnea.

The term *hyperpnea* is used to designate a condition of breathing in which the rate or the depth, or both, are increased. An individual in a state of hyperpnea may be unaware of any change in the breathing.

Polypnea signifies a rapid, shallow, panting type of respiration.

Apnea means a transient cessation of breathing.

ABDOMINAL AND COSTAL TYPES OF BREATHING

As stated above, abdominal breathing denotes a visible movement of the abdomen with the respirations; the abdomen is protruded during inspiration and recoils during expiration. Costal breathing, on the other hand, is characterized by pronounced rib movements. In a state of eupnea the abdominal type predominates in practically all animals. This means that in eupnea the diaphragm is the principal inspiratory muscle. With the onset of dyspnea, however, the costal type becomes prominent.

Whenever the movements of the abdomen are restricted, as by the use of tight clothing or binders, the costal type is prominent. It is also marked in painful conditions of the abdomen (enteritis, peritonitis).

METHODS OF RECORDING RESPIRATORY MOVEMENTS

The rate and amplitude of the respiratory movements may be registered in a number of ways. Some of these methods are applicable only under experimental conditions, while others are adapted for use not only in anesthetized experimental animals but also in intact animals and man. Of the different methods, the following may be mentioned:

1. A cannula or catheter is inserted into a pleural cavity between two ribs, care being taken to prevent the entrance of more than a small bubble of air through the opening. The catheter is then connected to some form of recording apparatus (tambour, piston recorder) arranged to write on a kymograph, usually in such a way that the downstroke of the lever will represent inspiration. At every inspiration the pressure in the pleural space is further reduced and the writing point descends; during expiration the writing point rises. This method really registers changes of intrathoracic pressure.

2. A tube is connected to a side arm of a tracheal cannula and then to a tambour or some other form of recorder. Inspiration results in a decrease of the pressure in the tube and recorder, causing a downward movement of the writing lever; expiration elevates the pressure in the tube and recorder, causing an upward movement of the writing point.

3. A pneumograph or a stethograph may be tied around the thorax and then connected to a recorder. Several forms of pneumograph have been devised. One of the simplest consists of a flexible coil spring incased in thin-walled rubber tubing. One end of the pneumograph is closed, and the other end is provided with an outlet to be connected with a tambour. The pneumograph is tied around the thorax in an appropriate location. Inspiration increases the capacity of the pneumograph, and the writing lever moves downward; expiration causes the opposite effect. A stethograph is essentially a hollow metal cylinder closed at each end with a rubber diaphragm. A string is fastened to the center of each membrane, and the apparatus is tied around the thorax. A tambour is connected by rubber tubing to a side tube of the stethograph. Inspiration causes the rubber diaphragms to be pulled

outward thus creating negative pressure in the stethograph, tube, and tambour; expiration causes the opposite effect.

4. A chest plethysmograph connected with a delicate recording spirometer may be used. The plethysmograph consists of a metal sheath under which there is a large rubber bag. The sheath and bag are fixed in place immediately over the thorax of a confined animal. When the thorax expands, some air is driven out of the slightly inflated rubber bag into the spirometer, whose inner cylinder is then elevated. This cylinder carries a writing point. Return of the thorax to the resting position causes the reverse action.

5. The Benedict-Roth type of basal metabolism apparatus may be used to obtain good records of the respiratory movements.

THE VOLUMES OF AIR RESPIRED

In man the volumes of air respired under different conditions of respiration may be measured with some form of gasometer. Hutchinson's spirometer or one of its modifications may be used. The spirometer works on the principle of the ordinary gasometer for storage of gas. The volume of air expired is determined by breathing into the spirometer; the volume inspired, by breathing out of the previously filled spirometer. The volume in both instances is read directly from a scale. Other forms of gasometer are available. The volumes may be reduced to S.T.P.

The terms given below are used to express the volumes of air inspired and expired under various conditions. Some of these values are not known for animals owing mainly to the obvious difficulties encountered in carrying out the determinations on these subjects. The figures given are only average; a wide range of variation is possible.

Tidal Air. By this term is meant the volume of air inspired or expired in one respiration. In man at rest it is about 500 cc.; in the horse about 6000 cc. (Gmelin); in the dairy cow while lying, 3100 cc., while standing, 3800 cc. (Hall and Brody); in the goat, about 310 cc. (Barcroft and co-workers, 1919).

Complemental Air. This term refers to the volume of air that can be inspired by the deepest possible inspiration after an ordinary inspiration. In man it amounts to some 2000 cc.; in the horse, 12,000 cc.

Supplemental or Reserve Air. This is the amount of air that can be expired by the deepest possible expiration after an ordinary expiration. In man it is about 1200 cc.; in the horse, 12,000 cc.

Vital Capacity. This is the volume of air that can be breathed out by the deepest possible expiration following the deepest possible inspiration: man, 3700 cc.; horse, 30,000 cc. It is evident that vital capacity equals complemental air plus tidal air plus supplemental or reserve air.

Residual Air. Following the driving out of the reserve air, the lungs are by no means collapsed; they still contain a good deal of air. This amount, the residual air, has been estimated in various ways. In man the average figure is about 1500 cc.; in the horse, probably about 12,000 cc.

Normal Capacity. This refers to the amount of air left in the lungs following a quiet expiration. It equals the reserve air plus the residual air: man, 2700 cc.; horse, about 24,000 cc.

Minimal Air. This is the small amount of air left in the lungs after the thorax is opened and the lungs are collapsed. It is the air that is entrapped in the alveoli when the terminal bronchioles collapse. It is a part of the residual air. The minimal air cannot be driven out even when the lungs are subjected to strong pressure. Because of the minimal air the lungs will float when placed in water.

The fetal lung is entirely solid; there is no air in it; it will sink when placed in water. A piece of lung from an animal that has breathed will float in water. This test may therefore be used to determine whether an anmial breathed after birth.

Minute Volume. The tidal air multiplied by the number of respirations per minute gives the respiratory minute volume, also known as the ventilation rate per minute. It can also be determined by measuring the volume of air inspired or expired per minute. Brody (1945) has studied the ventilation rate in relation to growth in horses, cattle, and swine. Lee and co-workers have studied tidal air, respiration rate, and respiratory minute volume as a part of their investigations on the reactions of animals to hot atmospheres (p. 542).

VENTILATION OF THE ALVEOLI

Until recently it was generally believed that the changes in size of the lungs accompanying breathing were attained chiefly by expansion and contraction of the alveoli. In this bellowslike manner the ventilation of the alveoli was supposed to be accomplished. Recent evidence supports the view that the alveoli change very little in size with the respirations (Macklin). The inspired air is accommodated mainly by an inspiratory lengthening and dilatation of the airway, or bronchial tree. It is believed that this increase of capacity involves principally the respiratory bronchioles and alveolar ducts, although the entire bronchial tree participates in the enlargement. During expiration the capacity of the airway decreases by a shortening and narrowing of its different portions, particularly the respiratory bronchioles and alveolar ducts. Ventilation of the alveoli, instead of being accomplished by a bellowslike expansion and recoil of their walls, is brought about by air currents from the alveolar ducts caused by the inrush of air into the bronchial tree. Entrance of air into the alveoli is facilitated by the widening during inspiration of the mouths through which the alveoli communicate with the chambers from which they spring. Diffusion gradients would help in the ventilation of the alveoli.

The musculature of the bronchial tree assists in the inspiratory increase of capacity of the airway by relaxing. It aids the expiratory decrease of capacity by contracting. The main forces concerned in inspiration and expiration have already been considered.

The musculature of the airway receives innervation from the vagi and the sympathetics (p. 196).

Dead Space. The respiratory passages extending from the external nares to the alveoli has long been designated as the *dead space.* When the alveoli were regarded as distensible sacs, it was customary to deduct from the tidal air the capacity of the dead space in order to determine how much of the inspired air actually entered the alveoli. Also the question whether the dead space could change in size was an active one. According to the view set forth above, the alveoli change in size very little during a respiratory cycle. The dead space in relation to alveolar ventilation has therefore taken on a less important aspect; and there can no longer be any serious doubt that the so-called dead space undergoes very considerable changes in capacity during a respiratory cycle.

It is the air in the alveoli that is in diffusion relations with the gases of the blood in the pulmonary capillaries. This subject is referred to again in Chapter IX.

INTRAPULMONIC PRESSURE

By intrapulmonic pressure is meant the air pressure in the lungs and the passages leading to them. Since there is free communication between the interior of the lungs, bronchi, trachea, etc., and the outside, it is clear that at every position of rest of the thorax the intrapulmonic pressure must be equal to the pressure of the atmosphere. During inspiration, however, the enlargement of the thorax and lungs is a little more rapid than the inrush of air. Therefore during this time the intrapulmonic pressure is slightly negative, that is, below the pressure of the atmosphere. In normal inspiration the negativity equals -2 to -3 mm. Hg. During expiration, on the other hand, the thorax and lungs return to the normal size a little more rapidly than the air is forced out. Therefore during this time the intrapulmonic pressure becomes slightly positive. The pressure changes can be measured by inserting a tube into a nostril or, better, a fine cannula through the wall of the trachea, and connecting the tube or cannula to a manometer.

When for any reason the air passages are partially or completely blocked, inspiration and expiration are accompanied by greater changes in intrapulmonic pressure than those given above. Incomplete blocking of the air passages is seen in pathological conditions such as rhinitis, edema of the glottis, and bronchitis. Complete blocking may be produced by closure of the glottis. An attempted inspiration with a closed glottis results in a fall in intrapulmonic pressure that varies directly with the amount of muscular effort expended. In strong inspiration the fall may be as much as −70 mm. Hg or more (man). An attempted expiration with a closed glottis leads to an elevation of intrapulmonic pressure, the amount depending on the strength of the expiratory effort. With a strong expiratory attempt, the elevation may be as much as 100 mm. Hg (man).

INTRATHORACIC PRESSURE

By intrathoracic or intrapleural pressure is meant the pressure in the thorax outside the lungs, that is, the pressure in the pleural spaces and mediastinum. It is the pressure to which the mediastinal organs are subjected and is, under ordinary conditions of breathing, negative. The explanation of the negativity lies in the fact that the lungs are actually smaller than the thorax which they occupy, yet owing to the pressure of the atmosphere on their interior and to their elastic properties, they are distended to fill completely all parts of the thorax not occupied by other structures. Therefore because the lungs are stretched and elastic, they *tend* to recoil. Their tendency to recoil counteracts the intrapulmonic pressure to a small extent, so that its full effect is not felt in the pleural spaces and mediastinum. The intrathoracic pressure therefore equals the intrapulmonic pressure minus the force of the elastic recoil of the lungs, and under any normal condition of breathing this relation holds. Intrathoracic pressure rises and falls with intrapulmonic pressure, but they are never quite the same; they always differ by the force of the elastic recoil of the lungs. It follows that at the end of inspiration, when of course the lungs are farther stretched and their tendency to recoil is greater, the intrathoracic pressure is less than at the end of expiration, when the lungs are less stretched. However, even at the end of the deepest possible expiration with the glottis open, the intrathoracic pressure is still negative by a small amount, for the lungs are far from collapsed; they still contain the residual air.

Measuring Intrathoracic Pressure. The magnitude of the negativity of the intrathoracic pressure may be measured in several ways. The simplest and most direct method is to insert a tube or catheter into a pleural space between two of the ribs, care being taken to prevent the entrance of more than a tiny bubble of air. The tube is then connected to a manometer, whereupon the liquid in the proximal limb of the manometer rises and that in the distal limb falls. The difference in the height of the two columns represents the negativity of the intrathoracic pressure. During inspiration the liquid is sucked farther up in the proximal limb of the manometer and during expiration it falls somewhat, but the intrathoracic pressure is still negative by a small amount. A graphic record of the pressure changes can be made.

Another method is to tie a tube into the trachea of a recently killed animal and connect it to a manometer of small bore. The thorax is then opened, whereupon the lungs tend to collapse, but this is prevented by the liquid in the manometer. The height to which the liquid is pushed equals the force of the elastic recoil of the lungs, and, as stated above, this equals the negativity of the intrathoracic pressure.

Data of Intrathoracic Pressure. In the sheep, dog, and rabbit Jakobson and Adamkiewicz (cited by M'Kendrick) found the negativity of the intrathoracic pressure to be −3 to −5 mm. Hg. Rosenthal (cited by M'Kendrick) found it to be −20 mm. Hg in the rabbit with the deepest inspiration. Heynsius obtained the following results on dogs: at the end of expiration, −4 mm. Hg; at the end of inspiration, −10 mm. Hg. In rabbits he found pressures of −2.5 mm. Hg and −4.5 mm. Hg. In recent work on sheep, Rangsit found intrathoracic pressures as follows: at the end of expiration, −8 mm. Hg; at the end of inspiration, −14 mm. Hg. In larger animals greater values doubtless prevail, although few determinations have been made. In the horse Bendele found the negativity of pressure in the pleural cavity to be, on the average, between −20 and −60 mm. Hg. The figures for the rabbit may be summarized as in the table. Atmospheric pressure of 760 mm. Hg is assumed.

PRESSURE CONDITIONS IN THE LUNGS AND THORAX OF RABBIT

	At end of quiet expiration	At end of quiet inspiration	At end of deepest possible inspiration
	mm. Hg	*mm. Hg*	*mm. Hg*
Intrapulmonic pressure.....	760	760	760
Negativity of intrathoracic pressure................	−2.5	−4.5	−20
Intrathoracic pressure......	757.5	755.5	740

Effect of Intrathoracic Pressure on the Mediastinal and Abdominal Organs. In view of the fact that the mediastinal organs are subjected to a pressure that can vary considerably, they must be affected by the pressure changes. When a strong expiratory attempt is made with a closed glottis, the elevation of pressure may be great enough to interfere markedly with the return of venous blood to the heart. This is seen in severe straining movements, which may lead to bulging of the veins of the neck and, in man, to visible congestion of the face. On the other hand, when an inspiration is attempted with a closed glottis, the negative pressure so induced distinctly hastens the return of blood to the heart via the great veins. In a like manner, negative pressure of considerable magnitude may be produced in the thoracic part of the esophagus. It is produced in the early stages of vomiting, and, as will be seen later, in ruminants it is the means of drawing food from the stomach into the esophagus in regurgitation.

In a similar though less pronounced way the negativity of the intrathoracic pressure affects the mediastinal organs in ordinary inspirations. This is spoken of as the aspiratory or suction-pump action of the thorax and is an aid to the return of blood and lymph to the heart.

When an expiration is attempted with a closed glottis, the abdominal pressure, as well as the pressure in the lungs and thorax, is elevated because the contraction of the abdominal muscles is opposed by the fixed diaphragm. The rise of abdominal pressure is transmitted equally in all directions, for the viscera act in this regard as if they were liquid; but the effect of the pressure is most noticeable on the pelvic organs because of their short connections with the outside. Emptying of these organs in defecation, urination, and parturition is therefore facilitated by the action of the *abdominal press.*

In the modified expiratory acts of coughing, laughing, talking, barking, lowing, etc., both intrathoracic and intrapulmonic pressures may be considerably elevated.

The Origin of the Negative Pressure. The lungs of the fetus are not distended; they completely fill the thorax but are solid. Therefore they do not exert any force of elastic recoil, and there is no negative pressure in the thorax. In the newborn animal the first inspiration causes the lungs to expand. Upon expiration they collapse, but not completely; a newly acquired tonus of the respiratory muscles prevents the thoracic cavity from returning to its fetal position. The respiratory and other skeletal muscles of the fetus in the uterus do not possess tonus. After birth, however, the skeletal muscles quickly acquire a certain degree of contraction or tonus. The tonus of the respiratory muscles causes the chest wall to assume a new resting position, so that the thoracic cavity is now larger than it was during intra-uterine life. The lungs are therefore not fully deflated upon expiration and a negative pressure develops in the pleural spaces. In life this tonus is never lost and the thorax never collapses as much as it would collapse if the tonus were absent. Furthermore, with the development of the animal the thorax grows faster than the lungs. This causes a gradual increase in the negativity of the intrathoracic pressure during growth.

PNEUMOTHORAX

Entrance of air into the pleural cavity produces the condition known as pneumothorax. The air may enter either through an opening to the outside in the thoracic wall or by way of a pulmonary lesion which has extended through the visceral pleura. If the opening remains patent (open pneumothorax), the lung on that side will collapse. The question arises as to whether collapse of one lung will lead also to collapse of the other. The answer is apparently not the same in all species. In the dog, according to Snyder, unilateral pneumothorax is impossible because of the free permeability of the mediastinum to air (and fluid). Changes of intrapleural pressure on one side are immediately followed by corresponding changes on the other side (Fig. 62). Bilateral pneumothorax therefore follows opening of the chest of the dog on one side. Evidently in intrathoracic operations in the dog, except perhaps experimental operations of very brief duration, artificial respiration by tracheal insufflation of air or oxygen would be necessary.

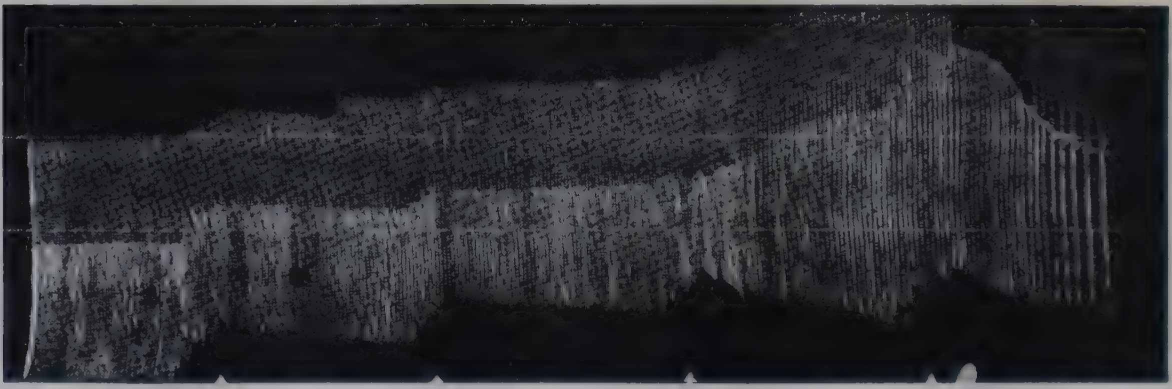

FIG. 62.—Intrapleural pressure changes on each side during the injection of air into the right pleural cavity of a dog. Ether anesthesia. The upper tracing is of left intrapleural pressure; the lower, right intrapleural pressure. The respective base lines represent atmospheric pressure. The little triangles at the lower margin of the graph indicate the times at which air in quantities of 200 cc. was injected into the right pleural cavity. Note that changes of pressure on the right side were accompanied by corresponding changes on the left side. Therefore the mediastinum of the dog is permeable to air. (Adapted from Snyder, *Archives of Surgery*, 1924, 8.)

In man the mediastinum is impermeable to air and fluids, but there is a significant displacement of the mediastinum to the opposite side in unilateral pneumothorax. This displacement results in similar pressure changes on the two sides, but they are not identical as in the dog (Snyder).

In the sheep limited observations by Rangsit indicate that unilateral pneumothorax is possible. A small opening into a pleural cavity on one side led to collapse of the corresponding lung, whereas the other lung did not collapse until an opening had been established on that side.

Little precise information is available on these questions as applied to large animals. Clinical observations suggest that the behavior of the lung when the chest is opened may not be the same as in small animals. F. Smith states that a small opening into the pleural cavity of the horse does not lead to collapse of the lungs but that a large opening does. Some reported cases of failure of the lung to collapse in large animals when a pleural cavity was opened might have been due to adhesions between the visceral and parietal pleurae.

Whether or not an animal will live following pneumothorax depends on the amount of air entering through the wound at each inspiration and on the ability of the animal to compensate by increased breathing. When the amount of air entering by the wound is so great that the animal cannot obtain its tidal-air requirements, even by the greatest possible augmentation of breathing, death from asphyxia will result.

RESPIRATORY VARIATIONS OF BLOOD PRESSURE IN SYSTEMIC ARTERIES

If a blood pressure tracing is examined, it will be seen to present at least two kinds of waves: short ones due to the systole and diastole of the heart, and long ones, due to the respiratory movements (Fig. 63). The waves caused by the heart's action were discussed in Chapter VI. Those produced by the respiratory movements have been the subject of numerous investigations and much discussion since they were first noticed by Stephen Hales in his classical experiments on blood pressure (1733), and it may be stated that there is as yet no complete agreement as to their cause and their relation to respiration. In

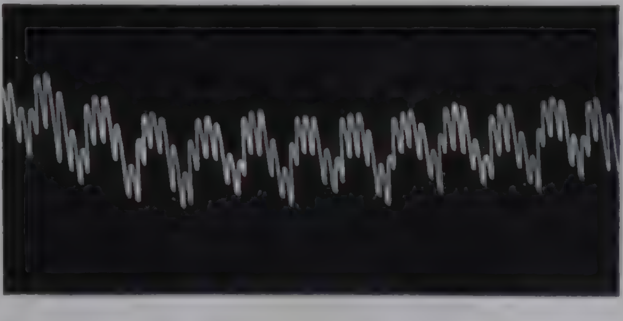

Fig. 63.—Blood pressure tracing from the carotid artery of a sheep to show respiratory waves of pressure. Mercury manometer. Local anesthesia. (Rangsit.)

some individuals the fall in mean pressure accompanies inspiration and the rise expiration. This may be said to be the uncomplicated condition. In other cases the reverse is true, inspiration being synchronous with a rise and expiration a fall. In still other instances a momentary fall and then a rise accompany inspiration, whereas a further brief rise and then a fall accompany expiration. Lastly, there is the condition in which inspiration is accompanied by a fall and then a brief rise, and expiration by a further rise and then a brief fall. There may be fundamental differences in the species in the behavior of the waves, although this is doubtful.

The simplest condition, a fall of blood pressure during inspiration and a rise during expiration, is caused by changes in the intrathoracic pressure with the respirations. During inspiration the negativity of the intrathoracic pressure increases and the great vessels in the thoracic cavity are expanded somewhat. This causes the pressure in them to fall. During expiration the vessels are less stretched and the blood pressure rises.

When there is cardiac acceleration during inspiration, as frequently occurs in dogs and sometimes in other animals, the increased output of the heart so induced favors a rise in mean pressure that overshadows the fall which the inspiration itself tends to produce; so that the final effect is a rise in mean pressure during inspiration. When cardiac acceleration is present but slight or delayed, there is likely to be during inspiration a brief fall and then a rise, and during expiration a further brief rise followed by a fall. The last condition, inspiratory fall and brief rise and expiratory rise and brief fall, is seen in deeper breathing and is explained in the following way: The augmented inspirations increase the venous return, and the systolic discharge of the right ventricle is thus increased. This, however, does not cause an increased output from the left ventricle for several beats and so the systemic blood pressure falls. Toward the end of inspiration, however, the flow of blood into the left side of the heart has increased sufficiently to cause an augmented ventricular output and hence a rise of systolic blood pressure. This rise continues to near the end of expiration, when the fall sets in. The increased capacity of the pulmonary vessels during inspiration contributes to the delay in the increased output of the left ventricle.

THE RATE OF RESPIRATION

This is the number of respirations per minute. The figures in the accompanying table give some idea of the range of variation of the rate in mature animals at rest and in man.

Rate of Respiration

Horse	8-16
Ox	10-30
Dairy cow	18-28
Sheep and goat	12-20
Pig	8-18
Dog	10-30
Cat	20-30
Fowl	15-30
Man	12-20

The rate of respiration is subject to numerous variations. Some of the factors responsible for the variations are body size, age, exercise, excitement, environmental temperature, pregnancy, and degree of fill of the digestive tract, especially the rumen.

Various febrile and other pathological conditions may affect the breathing rate.

Chapter IX

THE TRANSPORT AND EXCHANGE OF GASES

THE COMPOSITION OF INSPIRED AIR

THE composition of outdoor air is remarkably uniform from place to place over the earth's surface; this is true even in the vicinity of cities. The following figures show the composition of dry inspired air in volumes per cent:

O_2	CO_2	N_2
20.93	0.03	79.04

The figure for nitrogen includes 0.94 per cent of argon and traces of helium, krypton, neon, xenon, hydrogen, etc. These gases are generally believed to be of no physiological importance.

In confined spaces where the air is still, especially when combustion is taking place, decomposition of organic matter is going on, or animal life is present, the composition may vary somewhat from that given above.

EXPIRED AIR

Expired air contains oxygen, carbon dioxide, and nitrogen, but the proportion of the first two gases is not the same as in inspired air, which contains more oxygen and less carbon dioxide. Respiration results therefore in oxygen consumption and carbon dioxide production. Expired air from herbivores also contains considerable amounts of methane derived from carbohydrate fermentation in the alimentary canal. Likewise carbon dioxide is produced in the digestive tract of herbivores. Being eliminated largely through the lungs, it mixes with the carbon dioxide of metabolic origin. In some types of energy metabolism experiments on herbivorous animals during digestion, allowance must be made for the carbon dioxide derived from the alimentary canal. From studies on goats by Boycott and Damant, it appears that at least 10 per cent of the total carbon dioxide eliminated has this origin. In addition to variations in the composition of expired air due to fermentation in the digestive tract, variations may be brought about by changes in the kind of foodstuff being oxidized. Changes in the frequency or depth of respiration may bring about temporary changes in the composition of the expired air.

The following figures are fairly representative of the percentage composition of the dry expired air of man:

O_2	CO_2	N_2
16.29	4.21	79.50

In goats Barcroft and co-workers (1919) obtained the following results as a mean of many determinations:

O_2	CO_2
17.80	2.95

Zuntz and Hagemann made numerous determinations of the composition of the expired air of horses under different conditions. The following results are typical of those obtained from resting horses:

O_2	CO_2	N_2
15.97	4.74	79.29

A comparison of the composition of inspired air and of expired air is given in the table.

COMPOSITION OF DRY INSPIRED AND EXPIRED AIR

	O_2	CO_2	N_2
	per cent	*per cent*	*per cent*
Inspired air	20.93	0.03	79.04
Expired air	16.29	4.21	79.50
Difference	4.64	4.18	0.46

It is evident from this table that the volume of oxygen absorbed is greater than the volume of carbon dioxide eliminated. This accounts for the fact that the volume of nitrogen expired is *relatively* greater than the volume inspired. The reason why the volume of carbon dioxide given off is usually less than the volume of oxygen absorbed is that not all of the oxygen absorbed is used in the oxidation of carbon; some of it is used to oxidize other elements, chiefly hydrogen and sulfur.

The ratio $\frac{\text{volume } CO_2}{\text{volume } O_2}$ is called the respiratory quotient (R. Q.), and it varies with the kind of foodstuff being oxidized. This makes a determination of the respiratory quotient in metabolism studies an important procedure (p. 445).

In addition to the above-mentioned chemical changes in expired air, certain *physical changes* take place. Expired air is heated practically to the temperature of the body and is practically saturated with water vapor. Since the temperature of inspired air is usually distinctly below that of the body and the water vapor content is usually below saturation, breathing is the cause of heat loss from the body by reason of warming the inspiried air and evaporating water from the lungs, and is also the cause of water loss.

THE GASES OF THE BLOOD

Methods of Extraction. The blood contains the same gases as are found in the atmosphere—oxygen, carbon dioxide, and nitrogen—but in different proportions. There are several methods by which the blood gases may be extracted for analysis. The principles of two methods follow:

1. The gases may be extracted by exposing a sample of blood to the vacuum of a mercury pump, many forms of which have been devised. In all forms a torricellian vacuum is created in a glass chamber, and into this a known volume of blood (obtained without exposure to air) is allowed to run from another chamber. The blood boils in the vacuum and the blood gases are given off. By repeated evacuation, all gas may be extracted from the blood. The total volume of the gases recovered is then measured, and the volumes of carbon dioxide and oxygen are determined by absorption, respectively, with alkali and alkalized pyrogallol. What remains in the analyzer is nitrogen. The percentages of the different gases in the blood are then calculated (cc. of gas per 100 cc. of blood). Mercury pumps of this kind are not much used at present because of the large amount of labor required in the direct extraction of gases from the blood.

2. Measurement of the oxygen content of blood may be accomplished by the ferricyanide method. This depends on the fact that when a sample of hemolyzed blood is treated with potassium ferricyanide the whole of the oxygen is liberated and can be measured. The amount obtained in this way agrees very closely with the amount obtained by the mercurial gas-pump method. The ferricyanide method is used with some special form of extracting and measuring apparatus such as that of Van Slyke. In this apparatus both oxygen and carbon dioxide are released by the use of potassium ferricyanide and acid. Analysis of the gaseous mixture then follows.

The Volumes of the Blood Gases. These are shown for several species in the accompanying table. The figures mean volumes (cc.) of the gases per 100 volumes (cc.) of blood. The volume per cent of oxygen shows considerable intraspecific variations. This is because of variations in the hemoglobin content of the bloods. The volume of nitrogen in blood is constant at somewhat less than 1 cc. per 100 cc. of arterial or venous blood.

The volume of oxygen actually found in blood must not be confused with the volume the blood is capable of holding. The latter is the oxygen capacity of blood, and it varies directly with the hemoglobin content. Under ordinary conditions arterial blood is more than 95 per cent saturated with oxygen, that is, it contains more than 95 per cent as much oxygen as it would contain if all the hemoglobin were in the form of oxyhemoglobin.

Gases of the Blood

	Blood	O_2	CO_2	Remarks	Author
		vol. per cent	*vol. per cent*		
Dog....	Arterial	19.2	39.5		Schoeffer (cited by Haldane, 1922)
	Venous	11.9	45.3		
	Difference	7.3	5.8		
Goat...	Arterial	14.15	42.45	Average of 3 samples; non-lactating animals	Houchin and co-workers
	Venous*	9.14	49.00		
	Difference	5.01	6.55		
Goat...	Arterial	12.64	47.32	Average of 22 samples; lactating animals	Houchin and co-workers
	Venous*	7.24	53.89		
	Difference	5.40	6.57		
Man...	Arterial	18.97	49.68	Average of 10 cases	Harrop
	Venous	13.75	54.65		
	Difference	5.22	4.97		

* Mammary vein. The respiratory quotients (p. 445) in the goat data are greater than unity.

Percentage Utilization of Oxygen. It is evident from figures in the foregoing table that as the venous blood returns to the lungs it is far from being completely deprived of its oxygen. This means that as the arterial blood flows through the systemic capillaries only a part of the oxygen is abstracted for use in metabolism. However, when metabolism is distinctly increased, as in severe muscular work, the percentage of oxygen removed by the tissues may be much greater.

In man and the dog at rest the oxygen utilization by the tissues may amount to only 15 to 20 per cent of that available in arterial blood (Y. Henderson, 1925); in the goat, about 50 per cent (Barcroft and co-workers, 1919); in the cat, 31 per cent (Uyeno and Doi). In man during muscular work, on the contrary, the utilization may be as great as 75 per cent; yet in other individuals it may be much lower—almost or quite as low as during rest. In the latter individuals the increased oxygen demands by the tissues are met practically entirely by an increase in the minute volume of the circulation.

In anemias, where the percentage of oxygen in arterial blood is considerably reduced owing to a deficiency of hemoglobin, the percentage in the mixed venous blood is also reduced. In fact, under these conditions, venous blood may be almost entirely deprived of oxygen (Lundsgaard).

Quite as important as the oxygen difference between arterial and *mixed* venous blood is the oxygen difference between arterial blood and venous blood coming from individual tissues or organs. This arteriovenous oxygen difference, the volume of the blood flow through the organ per minute, and the weight of the organ furnish data for calculating the oxygen consumption per unit of weight of organ per minute.

GAS LAWS

Preceding the discussion of the transport and partial pressure of the blood gases, a review of the gas laws will be given. (See also Chapter I.)

Dalton's Law. According to this law, the partial pressure of a gas in a mixture of gases forms the same ratio with the total pressure as the volume of the gas with the total volume. From this it follows that the total pressure of a mixture of gases is equal to the sum of the pressures of the individual gases of which it is composed.

The atmosphere (dry) contains 20.93 per cent of oxygen, 0.03 per cent of carbon dioxide, and 79.04 per cent of nitrogen and has at sea level an average pressure of 760 mm. Hg. Air contains a variable amount of water vapor, which exerts a partial pressure in accordance with Dalton's law. Under ordinary conditions this pressure amounts to about 5 mm. Hg. In order to obtain the total pressure exerted by the other gases of the atmosphere, the partial pressure of water vapor is deducted from 760 mm. Hg.

The following calculation gives the partial pressure of oxygen in an atmosphere with the water-vapor pressure of 5 mm. Hg.

$$\frac{20.93}{100} \times (760 - 5) = 158 \text{ mm. Hg.}$$

The partial pressure of carbon dioxide is

$$\frac{0.03}{100} \times (760 - 5) = 0.23 \text{ mm. Hg.}$$

Dalton's law further states that when several gases are in contact with a liquid, each dissolves in the liquid independently of the presence of the others.

Boyle's Law. This states that, the temperature being constant, the pressure of a gas varies inversely as the volume. When the gas is compressed its pressure is increased in exact proportion, and the converse is true. The law may be stated another way by saying that at constant temperature the density of a gas varies directly as the pressure.

Henry's Law. This law states that, the temperature being constant, the amount of a gas dissolved in a liquid possessing no chemical affinity for the gas varies directly as the pressure of the gas in the surrounding medium. If a liquid such as water is brought into relation with a gas or a mixture of gases, they penetrate the liquid and become dissolved in it. The amount of a gas entering the liquid varies directly as the pressure of the gas in the surrounding medium. If the pressure is doubled, twice the amount of gas goes into solution; if it is halved, then half the gas in solution is given off. The pressure of the gas in the surrounding medium measures the pressure of the same gas in the liquid. If it is desired, therefore, to determine the pressure of a gas in a liquid, it is only necessary to determine the pressure of the gas in the medium to which the liquid is exposed.

AMOUNT OF GASES DISSOLVED IN BLOOD

The amounts of the three gases of the atmosphere that will go into physical solution in 1 cc. of blood at 38 degrees C. and at a pressure of 760 mm. Hg are: oxygen, 0.026 cc.; carbon dioxide, 0.526 cc.; and nitrogen, 0.013 cc. The figures show that the solubility of carbon dioxide in blood is 20 times greater than that of oxygen. From these figures and the partial pressures of the gases in the alveolar air, the amounts of the gases in physical solution in 100 cc. of blood can be calculated. The composition of alveolar air will be discussed later, but it may be stated that the average composition is as follows: oxygen, 14 per cent; carbon dioxide, 5.3 per cent; nitrogen, 74.5 per cent; and water vapor, 6.2 per cent.

The calculations of the amount of the gases in physical solution in 100 cc. of blood in the body are as follows:

Oxygen	$0.026 \times 100 \times 0.14 = 0.364$ cc.
Carbon dioxide	$0.526 \times 100 \times 0.053 = 2.79$ cc.
Nitrogen	$0.013 \times 100 \times 0.745 = 0.97$ cc.

Data already given indicate that only nitrogen is present in the blood in quantities corresponding to these figures. Therefore the other gases, oxygen and carbon dioxide, must exist in the blood in some form other than merely physical solution.

TRANSPORT OF THE BLOOD GASES

Nitrogen Transport and Significance. The amount of nitrogen in arterial and venous bloods is practically the same: about 1 volume per cent. This suggests that nitrogen is not used by the tissues; that it is of no physiological importance. The amount of nitrogen in the blood varies directly as its partial pressure in the air of the alveoli. This fact points to the conclusion that nitrogen is carried merely in physical solution in accordance with Henry's law. These are the generally accepted views regarding gaseous nitrogen in the blood.

Deep-sea divers and caisson workers breathe air under greatly increased pressures. The amount of the respiratory gases dissolved in the blood and tissues is increased in proportion to the increase in the partial pressures of the gases in the alveolar air. When the workers return to a normal pressure, the dissolved gases are now at a higher pressure with respect to the new environment. If the decompression is rapid, nitrogen bubbles may be released in the tissues and produce distension and aero-embolism. This condition is designated as *decompression sickness.* It can be avoided by slow decompression. Aviators may experience this condition when they ascend rapidly to high altitudes.

Oxygen Transport. In different species arterial blood yields some 15 to 20 cc. of oxygen per 100 cc. of blood. That this quantity could not be present merely in physical solution is indicated (1) by the large amount present, and (2) by the fact that the amount present is not directly proportional to the pressure of oxygen in an atmosphere to which the blood is exposed. (See dissociation curves.) It is known, in fact, that much the greater part of the oxygen in blood is carried in chemical combination with hemoglobin. It is generally assumed that 1 gm. of hemoglobin combines with 1.34 cc. of oxygen. A much smaller amount of oxygen, which varies directly with the partial pressure of oxygen in the alveoli, is carried in physical solution. The union between the hemoglobin in the blood of the pulmonary capillaries and the oxygen in the alveoli of the lungs, and the breaking up of oxyhemoglobin into oxygen and hemoglobin as the blood flows through the systemic capillaries, may be expressed by the reversible reaction,

$$\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO^2}.$$

Hemoglobin has therefore the property of acquiring oxygen in the lungs, where the oxygen pressure is high, and of unloading it in the tissues, where the oxygen pressure is low. As the hemoglobin leaves the lungs it is nearly saturated with oxygen, for it acquires when exposed to the pressure of oxygen in the alveolar air more than 95 per cent as much oxygen as it could hold if exposed to a full atmosphere of oxygen or more. Therefore breathing pure oxygen would cause only a small additional amount to enter the blood; the hemoglobin would take up only some 5 per cent more and a little more would go into physical solution in accordance with Henry's law.

Oxygen Dissociation Curves of Hemoglobin. The amount of oxygen that will be taken up by an aqueous solution of hemoglobin or by a sample of blood, at different oxygen pressures, has been studied by many investigators. The results may be so plotted that the figures along the ordinate represent the amount of oxygen taken up (expressed either as the percentage saturation of hemoglobin with oxygen or as volumes per cent of oxygen) and the figures along the abscissa the pressure of oxygen in millimeters of mercury. Curves so made are called oxygen dissociation curves of hemoglobin. They have been constructed for animals of many species and, as would be expected, there is much similarity in the appearance of the different curves.

The percentage saturation of hemoglobin at various partial pressures of oxygen can be determined as follows: Large cylindrical glass vessels called saturators (or tonometers)are used. Into the saturator a few cubic centimeters of the hemoglobin solution or the blood to be studied are introduced together with a nitrogen-oxygen mixture of known composition. The saturator is then rotated horizontally in a water bath at body temperature for several minutes, at the end of which time the oxygen and hemoglobin are in equilibrium. The solution or blood is then removed from the saturator, and the relative percentages of oxyhemoglobin and reduced hemoglobin are determined in a suitable apparatus. Suppose that six saturators each containing one of the following gaseous mixtures are used with an *aqueous solution* of hemoglobin:

1. Nitrogen and no oxygen
2. Nitrogen and oxygen at 5 mm. Hg pressure
3. Nitrogen and oxygen at 10 mm. Hg pressure
4. Nitrogen and oxygen at 20 mm. Hg pressure
5. Nitrogen and oxygen at 50 mm. Hg pressure
6. Nitrogen and oxygen at 100 mm. Hg pressure

Determination of the percentages of oxyhemoglobin and reduced hemoglobin in each case would give the following results (Halliburton):

Oxygen pressure in mm. Hg.	0	5	10	20	50	100
Per cent HbO_2 (that is, percentage saturation of Hb)	0	37	55	72	87	94
Per cent Hb (that is, percentage unsaturation of Hb)	100	63	45	28	13	6

The results may now be expressed in the form of a curve, as just stated; this is the oxygen dissociation curve of hemoglobin in aqueous solution, and, as shown in Fig. 64, it has the form of a rectangular hyperbola.

The oxygen dissociation curve of hemoglobin in actual blood is considerably different from that in water in that the former presents a decided double inflection or S-shaped appearance (Fig. 65). The reason for this shape of the curve is that oxyhemoglobin in actual blood releases its oxygen at a much higher surrounding oxygen pressure than it does in distilled water at body temperature. For example, at an oxygen pressure of 30 mm. Hg, hemoglobin in water is 80 per cent saturated with oxygen, whereas in blood it is only about 50 per cent saturated. The steep portion (55 to 25 mm. Hg) of the oxygen dissociation curve in blood means that oxygen is delivered to the tissues in quantity and at sufficient pressure, whereas the flatter portion above 75 mm. Hg means that hemoglobin is nearly saturated with oxygen through a rather wide range of variation in alveolar oxygen pressure.

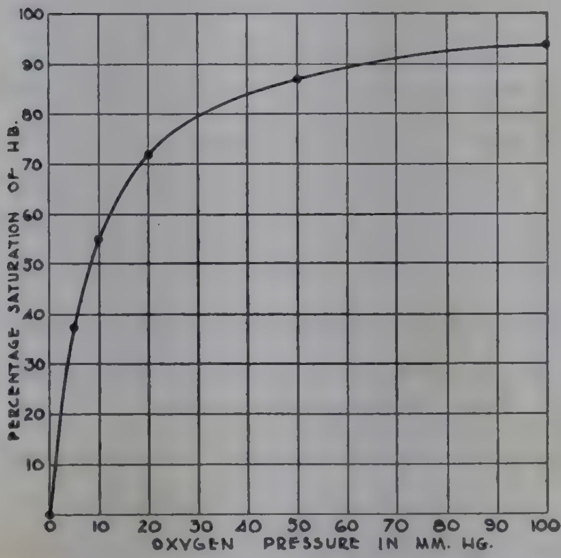

Fig. 64.—Oxygen dissociation curve of hemoglobin in aqueous solution. (Data of Halliburton.)

The principal factor accounting for the sharp declivity of the dissociation curve and thus the ease with which oxyhemoglobin in blood parts with its oxygen to the tissues is the entrance of acid products of metabolism into the blood from the tissues. The metabolite of most importance in this respect is carbon dioxide. At times other acids may be concerned, lactic for example. Conversely when carbon dioxide leaves the blood in the lungs, the taking up of oxygen by hemoglobin is facilitated. Hemoglobin in blood is therefore a very efficient oxygen carrier (Fig. 66).

Increased temperature is another factor which aids in the release of oxygen from oxyhemoglobin. Its importance under the conditions prevailing in the tissues is, however, not very great.

Carbon Dioxide Transport. A large amount of carbon dioxide (40

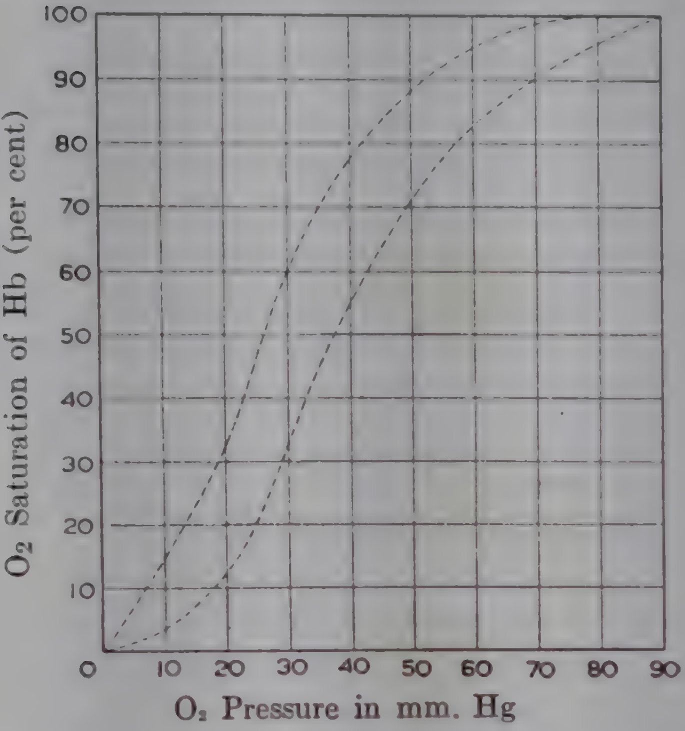

FIG. 65.—Range of variation in the oxygen dissociation curve of the blood of the cow as determined on several nonpregnant animals. The carbon dioxide pressure in the atmosphere to which the blood was exposed was 40-42 mm. Hg. (From Roos, *Journal of Physiology*, 1938, 92.)

to 60 volumes per cent) can be obtained from a sample of blood when exposed to a vacuum or when treated with acid. From figures already given it is evident that only about 2.8 volumes per cent can be held in

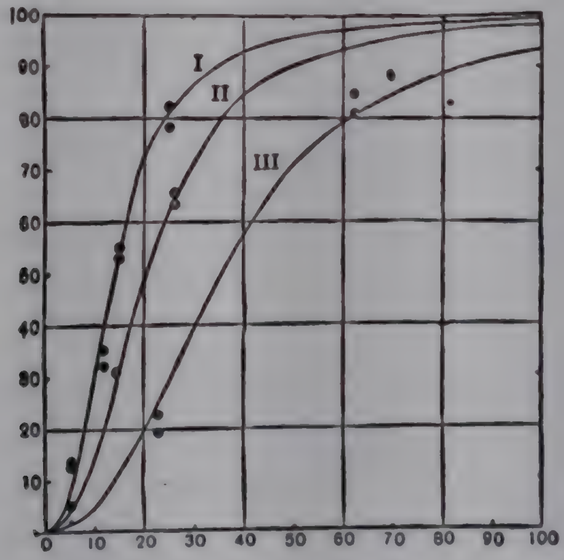

FIG. 66.—Oxygen dissociation curve of blood as affected by carbon dioxide. I, pressure of carbon dioxide, 3 mm. Hg; II, pressure of carbon dioxide, 20 mm. Hg; III, pressure of carbon dioxide, 90 mm. Hg. Ordinates show percentage saturation of hemoglobin; abscissas, oxygen pressure in millimeters of mercury. Note how the increasing pressure of carbon dioxide favors the release of oxygen and the decreasing pressure favors the uptake of oxygen. (Reproduced from the *Journal of Physiology*, **46**, page iv, by permission of the University Press, Cambridge, England.)

physical solution in the blood under the conditions prevailing in the body. Therefore the remaining amount must exist in some kind of chemical combination. This may be designated as the bound carbon dioxide. The fact that the carbon dioxide can be released by adding an acid to the blood suggests at once that the bound portion is held in the form of bicarbonate, and that most of it is so held there is general agreement. Work from a number of laboratories (Roughton) shows, however, that a physiologically important part of the carbon dioxide is bound in the blood in some way other than as bicarbonate.

In the discussions to follow, the transport of carbon dioxide as bicarbonate will be considered first, after which its transport in the form of other compounds will receive attention.

Carbon dioxide dissociation curves (Fig. 67) have been of material aid in studies on carbon dioxide transport in the blood. The method of their construction is similar to that described for oxygen dissociation curves, gases containing carbon dioxide under various partial pressures being used in the saturators together with the blood or the sodium bicarbonate solution to be equilibrated with the carbon dioxide. It has thus been found that the carbon dioxide dissociation curves of blood and of an aqueous solution of sodium bicarbonate (in equivalent amount) vary greatly (Fig. 68). When blood is exposed to a carbon-dioxide-free atmosphere all its carbon dioxide is given off. However, under similar conditions a bicarbonate solution gives off only half of its carbon dioxide:

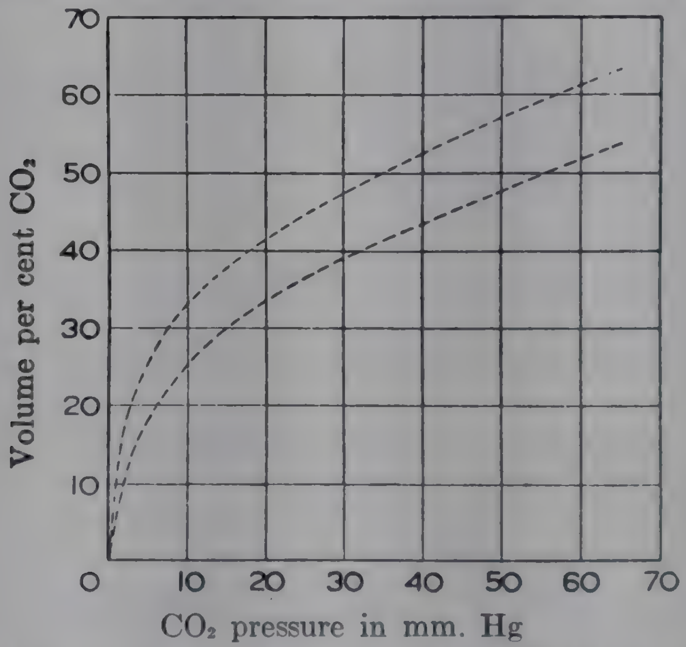

FIG. 67.—Range of variation in the carbon dioxide dissociation curve of the blood of the cow as determined on several nonpregnant animals. The blood was fully oxygenated. (From Roos, *Journal of Physiology*, 1938, 92.)

$$2NaHCO_3 \rightleftarrows Na_2CO_3 + CO_2 + H_2O.$$

The addition of a strong acid causes the evolution of an amount equal to that given off in the carbon-dioxide-free atmosphere. Clearly, if the carbon dioxide of the blood is actually held in the form of bicarbonate, some substance must be present in blood capable of causing all the carbon dioxide to be given off in a vacuum; capable of acting like acid added to a bicarbonate solution after it has lost all the carbon dioxide that it can, merely by exposing it to a vacuum. There are several reasons for believing that this acidlike substance exists in the corpuscles and not in the plasma. (1) The carbon dioxide dissociation curve of plasma is more like that of an aqueous bicarbonate solution than that of blood. Plasma, like the bicarbonate solution, requires the addition of acid to cause it to part with all its carbon dioxide. (2) The addition of corpuscles to plasma that has been exposed to a vacuum causes the evolution of the remaining part of its carbon dioxide in vacuo. The corpuscles therefore act like acid when they are added to plasma.

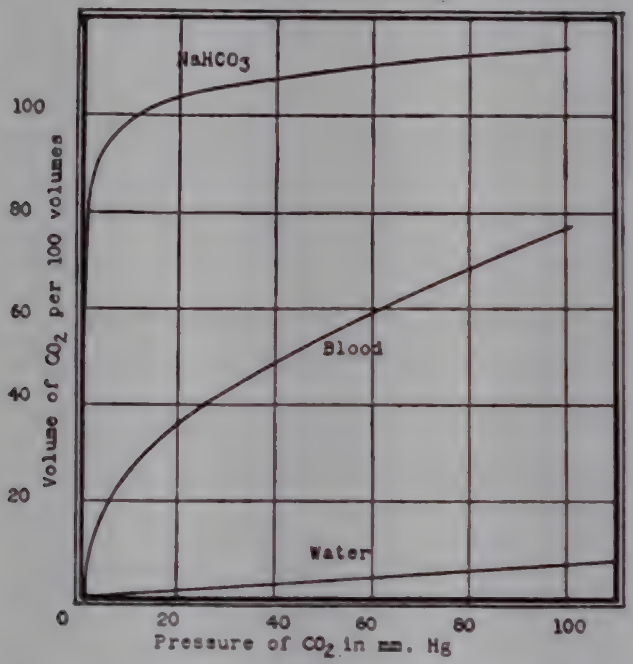

FIG. 68.—Carbon dioxide dissociation curves of sodium bicarbonate solution (0.0484 N) and of blood. Note that when the carbon dioxide pressure reaches zero, blood has given up all its carbon dioxide, whereas the bicarbonate solution has given up only one-half of its carbon dioxide. The lowest line shows the relation between the pressure of carbon dioxide to which water is exposed and the amount of carbon dioxide that the water will hold in physical solution. (From Evans' *Recent Advances in Physiology*, Ed. 4, published by P. Blakiston's Son and Company, Inc.)

The dissociation curve of carbon dioxide in blood shows that, while this acidlike action of the corpuscles favors complete liberation of carbon dioxide with decreasing pressure of the gas, it does not hinder the taking up of carbon dioxide by the blood with increasing pressure. This property makes blood from the physiological point of view a very efficient carrier of carbon dioxide. It may now be inquired what there is in corpuscles that gives blood this important property. The erythrocytes contain the weak acids hemoglobin and monobasic dihydrogen phosphate. These exist in the corpuscle in combination with bases, chiefly K, forming KH_2PO_4 and KHb. The base may be removed from such combinations by a stronger acid such as carbonic provided it can penetrate the corpuscle. When carbon dioxide enters the blood much of it at once passes into the erythrocytes, where it is hydrated to form carbonic acid:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-.$$

Some of the carbonic acid so formed reacts with K^+ yielded by hemoglobin, which, because it has parted with its oxygen to the tissues, is now a weaker acid than carbonic:

$$H_2CO_3 + KHb \rightleftarrows KHCO_3 + HHb.$$

The corpuscular membrane is impermeable to K^+ but not to HCO_3^- which, continuing to accumulate in the erythrocytes, upsets the Donnan equilibrium between them and the plasma. In order to restore this equilibrium HCO_3^- diffuses from the red corpuscles into the plasma and Cl^- from the plasma into the corpuscles. This is known as the *chloride shift*.

The ability of reduced blood to take up carbon dioxide is much greater than that of oxygenated blood. This is because hemoglobin is a weaker acid than oxyhemoglobin; therefore as the reaction

$$HbO_2 \rightleftarrows Hb + O_2$$

takes place during the passage of blood through the systemic capillaries hemoglobin parts more readily with K^+ for the binding of carbon dioxide. The K^+ which hemoglobin thus yields is believed to account for at least half the carbon-dioxide-carrying power of the blood. In the lungs the reverse process takes place: hemoglobin becomes loaded with oxygen and its acidity is thereby increased. This enables hemoglobin to recover the K^+ that it lost. Cl^- then diffuses back to the plasma and HCO_3^- passes from the plasma to the corpuscles. Carbonic acid is formed and then dehydrated,

$$H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows CO_2 + H_2O,$$

and carbon dioxide and water pass into the plasma. Thus carbon dioxide is released.

It has already been stated that the unloading of oxygen from the blood in the capillaries is aided by the intake of carbon dioxide (acid) from the tissues and that the release of carbon dioxide in the lungs favors oxygenation of the blood. Now it is seen that the reverse is true: unloading of oxygen in the tissues favors acquisition of carbon dioxide by the blood, and oxygenation of the blood in the lungs hastens the release of carbon dioxide. The mechanisms of the acquisition, transport, and release of oxygen and carbon dioxide are therefore remarkably interdependent.

In addition to the reactions given above, less important ones take place: KH_2PO_4 in the erythrocytes yields some alkali for the neutralization of carbonic acid, and the plasma proteins resemble hemoglobin in that they are combined with alkali, which can be used to neutralize acids, such as carbonic, entering the blood. However, it has been shown that the plasma proteins are responsible for only about one-tenth of the buffer power of blood.

Work within recent years, reviewed by Roughton, has enlarged our knowledge of carbon dioxide transport along two chief lines. In the first place it is now definitely known that the reversible reaction,

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-,$$

which takes place in the red corpuscles, is catalyzed by the presence in them of the enzyme *carbonic anhydrase*, a zinc-protein compound. It has been shown that were this enzyme not present, the taking up and giving off of carbon dioxide in respiration, in so far as this reaction is concerned, would be much too slow for physiological needs. Carbonic anhydrase has a fairly wide distribution in nature. It has been demonstrated in many tissues, but is lacking in some. It is not present in tissue fluid or blood plasma. The gastric mucosa, pancreas, and nervous system contain considerable amounts, but its significance in these locations is not clear. Carbonic anhydrase occurs in the kidney cortex and is thought to be a part of the mechanism for the formation of acid urine. It is present in the oviducts of birds and is believed to be concerned in the formation of egg shells. Sulfanilamide and other sulfonamide drugs are inhibitors of carbonic anhydrase.

In the second place, there is a growing mass of evidence which points to the conclusion that an important part of the bound carbon dioxide of the blood is carried in some form other than bicarbonate or carbonic acid. Hemoglobin is one of the substances with which this nonbicarbonate quota of carbon dioxide is combined. Thus the view of a number of the older investigators that hemoglobin is directly concerned in the transport of carbon dioxide is confirmed. The nature of the combination between carbon dioxide and hemoglobin has been investigated. It appears than an NH_2 group of the hemoglobin molecule is the place of attachment of the carbon dioxide. The compound is referred to as a carbamino compound, and is sometimes designated as carbhemoglobin. The carbamino reaction is very rapid; no enzyme is required. The reversible reaction between hemoglobin and carbon dioxide may be expressed as follows:

$$HHbNH_2 + CO_2 \rightleftarrows HHbNHCOOH.$$

The carbamino-bound carbon dioxide accounts for 10 per cent or less of the total carbon dioxide of the blood. Of the carbon dioxide released from the blood in the lungs, the carbamino reaction probably accounts for 25 per cent under resting conditions. Its significance in carbon dioxide transport is therefore very considerable.

THE EXCHANGE OF GASES IN THE LUNGS AND TISSUES

The subjects now to be considered are the exchanges between the air in the lungs and the blood in the pulmonary capillaries, and between the blood in the systemic capillaries and the tissues. In seeking an explanation of the forces governing these exchanges, it is logical to think first of diffusion, and the theory of respiration which holds that diffusion furnishes an adequate explanation is called the *physical theory*. From the facts about to be presented it will be seen that the conditions in the body are such as to make certain that diffusion occurs. Modern opinion holds, in fact, that diffusion forces are adequate to explain the gaseous exchanges both in external and internal respiration.

At one time it was believed by some investigators that the lung epithelium secretes oxygen from the alveoli into the blood of the pulmonary capillaries, at least at high altitudes, where the environmental oxygen pressure is low (Haldane). It was held that under such conditions the oxygen pressure in the arterial blood leaving the lungs could be higher than the oxygen pressure in the alveoli of the lungs. Many workers have failed to confirm the *secretory theory* of respiration (see Barcroft, Krogh, Campbell).

Alveolar Air. In order to calculate the partial pressures of the gases in the alveoli of the lungs—the gases to which the blood is exposed—it is necessary to know the composition of alveolar air. This may be determined either directly (Haldane) or indirectly by calculations based on the composition of expired air (Krogh and Lindhard).

The direct method is simple in principle. It was devised for application to man, although modifications of it have been applied to animals.

A piece of hose about four feet in length and one inch in diameter is equipped at one end with a mouthpiece. Near the mouthpiece an evacuated gas sampling tube or an all-glass syringe is connected to the hose. The subject breathes normally through the hose for a while, following which he makes a deep expiration and closes the mouthpiece with the tongue. The sampling tube is then opened and air rushes in, or air is drawn in by pulling out the plunger of the syringe. This is alveolar air, or, perhaps more precisely, air from the alveolar ducts. Its composition is determined by gas analysis. The partial pressures are then calculated. Results so obtained vary somewhat in different individuals. However, in the same individual under the same conditions, the results are said to be strikingly constant from time to time.

The figures in the table show the composition and the partial pressure of the gases in alveolar air of man.

ALVEOLAR AIR

	Composition	Partial Pressure
	per cent	*mm. Hg*
Oxygen	14	106
Carbon dioxide	5.3	40
Nitrogen	74.5	567
Water vapor	6.2	47

Edds has studied the composition of alveolar air of animals (horse, cow, sheep, goat, dog) by the direct method. Connection between the respiratory passages of the animal and the tube was effected by means of a mask for the muzzle. Results similar to those just given were obtained. However, there were some differences, for which the original paper should be consulted.

The Partial Pressure of Gases in the Blood and Tissues. The partial pressure of the gases in alveolar air having been noted, it is next in order to inquire into the partial pressure of oxygen and of carbon dioxide in arterial and venous bloods and in the tissues.

The difference between the actual amount of a gas in a liquid and its partial pressure in the liquid should be kept in mind. Thus the *amount* of oxygen per 100 cc. of arterial blood is 15 to 20 cc., whereas the *partial pressure* of oxygen in arterial blood is about 100 mm. Hg.

In Arterial and Venous Blood. The direct methods of determining the partial pressure of gases in the blood are based on the principle that the partial pressure of a gas in a liquid is the same as that of the gas in a gaseous mixture with which the liquid is in equilibrium. A small bubble of gas (air, nitrogen) is brought into contact with a large amount of blood, and gaseous equilibrium between the bubble and the blood is allowed to take place. The bubble, which is small enough not to change significantly the partial pressures of the gases in the much larger volume of blood, is then withdrawn into an apparatus for micro-analysis of gas and its percentage composition determined. From the percentages the partial pressures are calculated.

For arterial blood the foregoing may be accomplished by inserting a *tonometer* into the course of the artery. Krogh (1910) has devised several forms, one of which will be described briefly. It consists essentially of a T-shaped cannula which can be inserted in the course of a blood vessel (Fig. 69). The upright tube of the cannula communicates with an equilibration chamber, and this in turn with an apparatus for micro-analysis of gas. A bubble of air is introduced into the chamber, through which some of the blood in the cannula is diverted. Diffusion now takes place between the gases of the bubble and of the blood. After a few minutes equilibrium is established. The bubble is withdrawn from the tonometer into the apparatus for micro-analysis where its

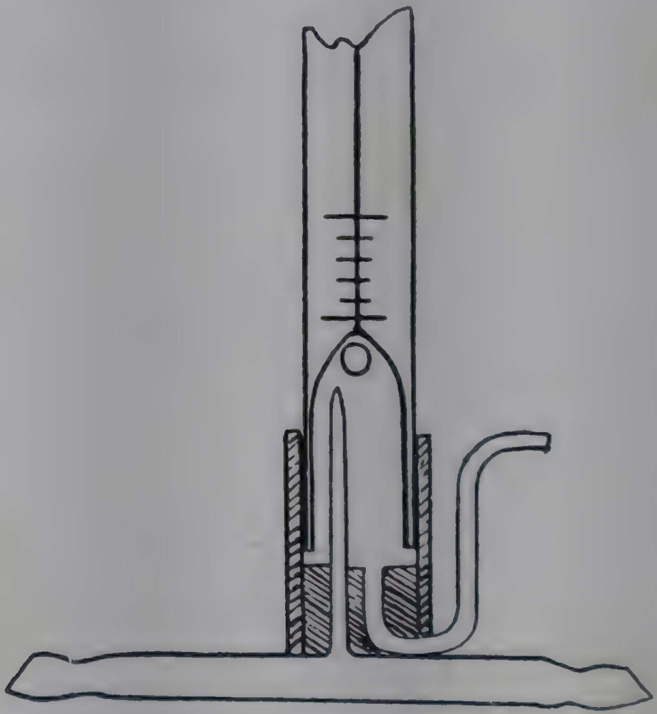

Fig. 69.—A microtonometer, with cannula for insertion into a blood vessel. Blood flows through the cannula, but a continuous sample of it enters the chamber of the tonometer through the upright tube and leaves through the curved tube at the right. After equilibrium has been established between the gases of the blood and the gases of a bubble previously introduced into the chamber, the bubble is withdrawn into an apparatus (only the lower part of which is shown in the diagram) for analysis. (From Krogh and Krogh, *Skandinavisches Archiv für Physiologie*, **23**.)

oxygen and carbon dioxide percentages are determined. The partial pressures are then calculated.

Another method is to obtain a large sample of blood by puncture of an artery or the left ventricle and to equilibrate it with a bubble of nitrogen. An all-glass syringe with an oiled plunger may be used as a tonometer.

For purposes now under consideration, it is necessary, in the determination of the partial pressures of the gases in venous blood, to turn to a location whose venous blood represents the body as a whole and not simply an organ or part of the body. Krogh's tonometer may be inserted into a pulmonary artery, or samples of mixed venous blood may be drawn into a syringe tonometer by puncture of the right ventricle or by catheterization of the right atrium via a jugular vein.

In Tissues. In modern work the partial pressures of gases in the tissues (Campbell) are estimated by injecting a gas (usually nitrogen) under the skin or into a body cavity, allowing some days to elapse, removing a sample of the gas, and determining its composition in a gas-analysis apparatus. From the percentage composition the partial pressures are calculated. After a time the gases of the gas depot and the gases of the tissues reach equilibrium, and the partial pressures of the gases in the depot are considered to be the same as those of the gases just outside the body cells. Actually, in this method, the whole animal serves as a tonometer.

Summary. Figures in the accompanying table illustrate partial pressures of the gases in arterial and venous blood, in the tissues, and in alveolar air (p. 226). Venous blood enters the pulmonary capillaries with its oxygen at a partial pressure of 40 to 50 mm. Hg (hemoglobin about 75 per cent saturated with oxygen) and its carbon dioxide at a partial pressure of 46 mm. Hg. Since the partial pressure of oxygen in alveolar air is about 106 mm. Hg and that of carbon dioxide 40 mm. Hg, diffusion of oxygen will occur from the alveoli to the blood and diffusion of carbon dioxide from blood to alveoli. The membrane across which the exchange occurs is composed of the respiratory epithelium and the capillary endothelium. The blood coming to the lungs therefore loses carbon dioxide and gains oxygen. A given particle of blood remains in a pulmonary capillary somewhat less than one second. The area of the membrane presented by the alveoli and pulmonary capillaries is very great, being many times larger than the body surface area. As the arterialized blood leaves the lungs to be pumped out to all parts of the body, its hemoglobin is more than 95 per cent saturated with oxygen. The partial pressure of oxygen in arterial blood is nearly the same as that of oxygen in alveolar air. In the case of carbon dioxide the pressures are the same. These facts emphasize the nearly perfect gaseous equilibrium that exists between alveolar air and arterial blood. The pressure head for the diffusion of carbon dioxide in the lungs is much less than that for the diffusion of oxygen. This, however, is not a hindrance to the effective diffusion of carbon dioxide, since the diffusion rate of carbon dioxide in water and tissues is some 25 times that of oxygen.

PARTIAL PRESSURES OF GASES IN ALVEOLAR AIR, BLOOD, AND TISSUES

	O_2	CO_2	N_2	H_2O
	mm. Hg	*mm. Hg*	*mm. Hg*	*mm. Hg*
Alveolar air	106	40	567	47
Arterial blood	100	40	567	47
Venous blood	40–50	46	567	47
Tissues	20–40	50	567	47

(Data from Campbell, 1931.)

On entering the systemic capillaries the arterial blood encounters a region of low oxygen pressure (20 to 40 mm. Hg) and relatively high carbon dioxide pressure (50 mm. Hg). Diffusion therefore takes place across the capillary endothelium. Oxygen diffuses from erythrocytes to plasma, from plasma to tissue fluid, and from tissue fluid to cells. There is thus a continuous stream from the store in the red corpuscles to the tissues. Carbon dioxide diffuses from cells to tissue fluid, from tissue fluid to plasma, and from plasma to red corpuscles. In the plasma and erythrocytes it is taken up by the carbon dioxide carriers.

The partial pressures of nitrogen and water vapor are the same (567 mm. Hg and 47 mm. Hg) in alveolar air, blood, and tissues.

Experimental work has shown that the gaseous exchange across the placenta takes place by diffusion.

ANOXIA

Anoxia[1] is a term used to signify a condition of oxygen want in the body. Anoxia is a serious threat to the organism. The biological mechanisms are stopped by anoxia and if the condition is prolonged the machinery is severely damaged or completely wrecked.

Four types of anoxia are generally recognized: (1) *Anoxic anoxia*, in which the arterial blood is insufficiently saturated with oxygen because of a low partial pressure of oxygen in arterial blood. (2) *Anemic anoxia,* in which there is a decrease in the oxygen capacity of the blood because of a shortage of functioning hemoglobin. (3) *Stagnant anoxia,* also known as *ischemic anoxia,* in which the blood flow through the whole organism or a tissue is diminished. (4) *Histotoxic anoxia,* in which the tissue cells are poisoned and therefore cannot make proper use of the oxygen supplied to them.

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[1] Since the term anoxia literally means "without oxygen," some writers prefer the term hypoxia. Anoxemia, or hypoxemia, means a deficient amount of oxygen in the blood. The term asphyxia should be used for "a condition of anoxia combined with an increase of carbon dioxide tension in the blood and in the tissues" (Van Liere).

Anoxic Anoxia. This condition is characterized by a low partial pressure of oxygen in arterial blood, and it therefore affects the body as a whole. It is seen at high altitudes, during the breathing of inert gases and anesthetics, in pneumonia and other pulmonary conditions that interfere with the passage of oxygen into the blood, in failure of the respiratory movements, etc.

Anoxic anoxia may be produced experimentally in a number of ways: (1) By use of a bag or spirometer for rebreathing air or oxygen mixed with an inert gas. The oxygen is used up by the subject and the carbon dioxide is absorbed by soda lime or caustic alkali. The volume of gas in the bag decreases and the percentage and partial pressure of oxygen fall, but the total pressure of the gases remains unchanged. (2) By breathing air or oxygen gradually diluted with an inert gas such as nitrogen or helium. (3) By use of a chamber in which a low atmospheric pressure can be established by means of an air pump.

Anemic Anoxia. In this type there is a decrease in the oxygen capacity of the blood because of a shortage of functioning hemoglobin. The partial pressure of oxygen is normal and the percentage saturation of the hemoglobin that is present is also normal. But an insufficient volume of oxygen is delivered to the tissues. Anemic anoxia is seen after hemorrhage, in anemias, and in conditions in which a part of the hemoglobin is changed to methemoglobin or is combined with carbon monoxide.

Stagnant Anoxia. In this condition the blood flow through the whole organism or some part of it is diminished because of general or local failure of the circulation. The oxygen content of the arterial blood is normal but the tissues fail to receive enough oxygen because of the diminished blood flow. In its slow movement through the capillaries the blood gives off a larger proportion of its oxygen than normal. Hence the venous blood shows a low oxygen content.

Histotoxic Anoxia. In this form of anoxia the tissues are unable to utilize oxygen in the physiological oxidations. The amount and the partial pressure of oxygen are normal in arterial blood and, because of the failure of the tissues to use oxygen, above normal in venous blood. Histotoxic anoxia is typically seen in cyanide poisoning, and occurs to some extent during the action of alcohol and anesthetics.

The Effects of Anoxia. As regards the rapidity with which anoxia develops, three types are distinguished: fulminating, acute, and chronic. The effects of anoxia depend to a large extent on the speed with which the condition develops. The fulminating type comes on very quickly, as when an animal inhales a physiologically inert gas such as nitrogen or helium. Under these conditions the oxygen supply in the blood falls rapidly and unconsciousness occurs in a minute and a half or less. Fulminating anoxia is the cause of death in sudden failure of the circulation such as occurs in ventricular fibrillation.

Acute anoxia is less severe and more slowly developing than the foregoing. It may be produced experimentally in several ways (p. 231). Under practical conditions it may occur in people or animals living at high altitudes, in mountain climbers, and in aviators. The symptoms are not unlike those seen in intoxication from alcohol, which is a form of histotoxic anoxia. Acute anoxia probably affects all parts of the body, but the central nervous system, heart, and respiratory system show the most evident effects.

Chronic anoxia may be produced by prolonged living at high altitudes. The symptoms resemble fatigue. Chronic mountain sickness is the term applied to this condition. After some weeks the physiological adjustments and compensations known as acclimatization usually occur.

Further information on anoxia may be found in the monograph by Van Liere. Chronic mountain sickness is discussed in a review by Monge.

THE EFFECTS OF OXYGEN AT INCREASED PRESSURE

Increased pressure of oxygen in a respiratory gas may be brought about in several ways: (1) By using hyperoxygenated air or pure oxygen at normal barometric pressure. Thus oxygen pressures up to 100 per cent of an atmosphere can be attained. (2) By using ordinary air under compression. In this way oxygen pressures greater than one atmosphere may be produced. (3) By using hyperoxygenated air under compression. In this way very high oxygen pressures can be obtained.

Only the first method will receive further consideration here. It might be supposed that the breathing of oxygen under increased pressure (not in excess of one atmosphere) would increase the metabolic rate. However the balance of evidence favors the view that the metabolic rate is not a function of the oxygen partial pressure (Bean). Many experiments have revealed, however, that continuous breathing for some hours of oxygen in concentrations greater than 60 to 70 per cent of an atmosphere, at atmospheric pressure, causes pulmonary damage, adverse changes in the tissue enzyme systems, other disorders, and even death if the exposure is further prolonged (Bean).

The question of oxygen toxicity has an important bearing on oxygen inhalations for therapeutic purposes. *Oxygen therapy* is often of value in pathological conditions accompanied by reduced rates of oxygen diffusion through the lungs: pulmonary edema, bronchitis, pneumonia. It is also useful in carbon monoxide poisoning because the increased partial pressure of oxygen in the blood aids in the dissociation of HbCO (p. 39). However, it is evident from the foregoing that the concentration of oxygen in the respiratory mixture should not be greater than 60 to 70 per cent of an atmosphere if the exposure is to be long continued.

PHYSIOLOGICAL OXIDATIONS[1]

How do living cells cause fats, carbohydrates, and proteins to unite with oxygen, whereby energy and heat are produced and carbon dioxide, water, and urea are released as end-products? Although it has been known for many years that living tissues contain enzymes which are capable of accelerating the oxidation of gum guaiac, phenols, and aromatic amines, nevertheless the chemistry of physiological oxidations has not been generally understood until recently.

Oxidation reactions are reversible and can be spoken of either as oxidations or reductions, depending upon the side from which equilibrium is being approached. One can define oxidation as a loss of electrons, as addition of oxygen, or as removal of hydrogen. In living things oxidation is brought about by enzymes known as oxidases. These can be divided into class I, the aerobic oxidases, or enzymes which activate oxygen so that the oxygen is used more or less directly to oxidize the substrate, and class II, the dehydrogenases, or enzymes which activate the hydrogen of the oxidizable substance and thus bring about its removal. A few examples of both classes are listed below:

Class I	Class II
Aerobic Oxidases	*Dehydrogenases*
Ascorbic acid oxidase	Xanthine dehydrogenases
Cytochrome oxidase	*d*-Amino acid oxidase
Polyphenol oxidase	Succinic dehydrogenase
Tyrosinase	Malic dehydrogenase
	Robison ester dehydrogenase

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[1] Contributed by Dr. J. B. Sumner.

In addition to the two types of enzymes listed above there exists the enzyme peroxidase. This resembles the aerobic oxidases but differs in the respect of being unable to make use of gaseous oxygen. Peroxidase acts only if hydrogen peroxide, or some other peroxide, is present to supply oxygen. Yet another enzyme, catalase, while not an oxidase, is closely connected with physiological oxidations, since it has the property of destroying hydrogen peroxide, a by-product of many oxidative reactions. By this means cells are protected from injury or destruction.

The aerobic oxidases contain either iron or copper, and their ability to transfer gaseous oxygen to their respective substrates is connected with the changes of valence of these heavy metals. The aerobic oxidases can be considered to consist of a protein part united with a nonprotein part which contains the heavy metal. This prosthetic group is of low molecular weight. The dehydrogenases likewise are made up of a protein part (apoenzyme) united with a nonprotein part (coenzyme) to form the complete enzyme (holoenzyme). In the case of the aerobic oxidases the prosthetic groups are rather firmly united with the protein components, but with the dehydrogenases the union is sometimes so incomplete that the coenzyme is largely in the free state. A few examples are given below:

Holoenzyme	*Apoenzyme*	*Coenzyme*
Peroxidase	Protein	Hematin
Diaphorase	Protein	Isoalloxazine adenine dinucleotide
Alcohol dehydrogenase	Protein	Codehydrase I
Old yellow enzyme	Protein	Riboflavin phosphate

In the living cell the oxidizing enzyme acts in conjunction with many other oxidizing enzymes as well as various oxygen carriers. Accordingly, each individual enzyme can be likened to a person in a bucket brigade. Oxidation consists of a large number of consecutive stages. This is illustrated by the reactions shown below:

I. Glucose-6-phosphate + protein-codehydrase II = phosphohexonic acid + protein-reduced codehydrase II.

II. Protein-reduced codehydrase II + cytochrome + cytochrome reductase = protein-codehydrase II + reduced cytochrome + cytochrome reductase.

III. Reduced cytochrome + cytochrome oxidase + O_2 = cytochorme + cytochrome oxidase + $2H_2O$.

Here the dehydrogenase removes hydrogen from glucose-6-phosphate (oxidizable substance). The hydrogen is then converted into hydrogen ions and electrons are given to cytochrome. The reduced cytochrome and the hydrogen ions are then oxidized if gaseous oxygen is present. The end-products are phosphohexonic acid and water.

Another illustration of an oxidation is shown below:

I. Ethyl alcohol + alcohol dehydrogenase (protein-codehydrase I) = acetaldehyde + reduced alcohol dehydrogenase.
II. Reduced alcohol dehydrogenase + diaphorase = alcohol dehydrogenase + reduced diaphorase.
III. Reduced diaphorase + carrier = diaphorase + reduced carrier.
IV. Reduced carrier + O_2 = H_2O_2 + carrier.
V. H_2O_2 + catalase = H_2O + $\frac{1}{2}O_2$ + catalase.

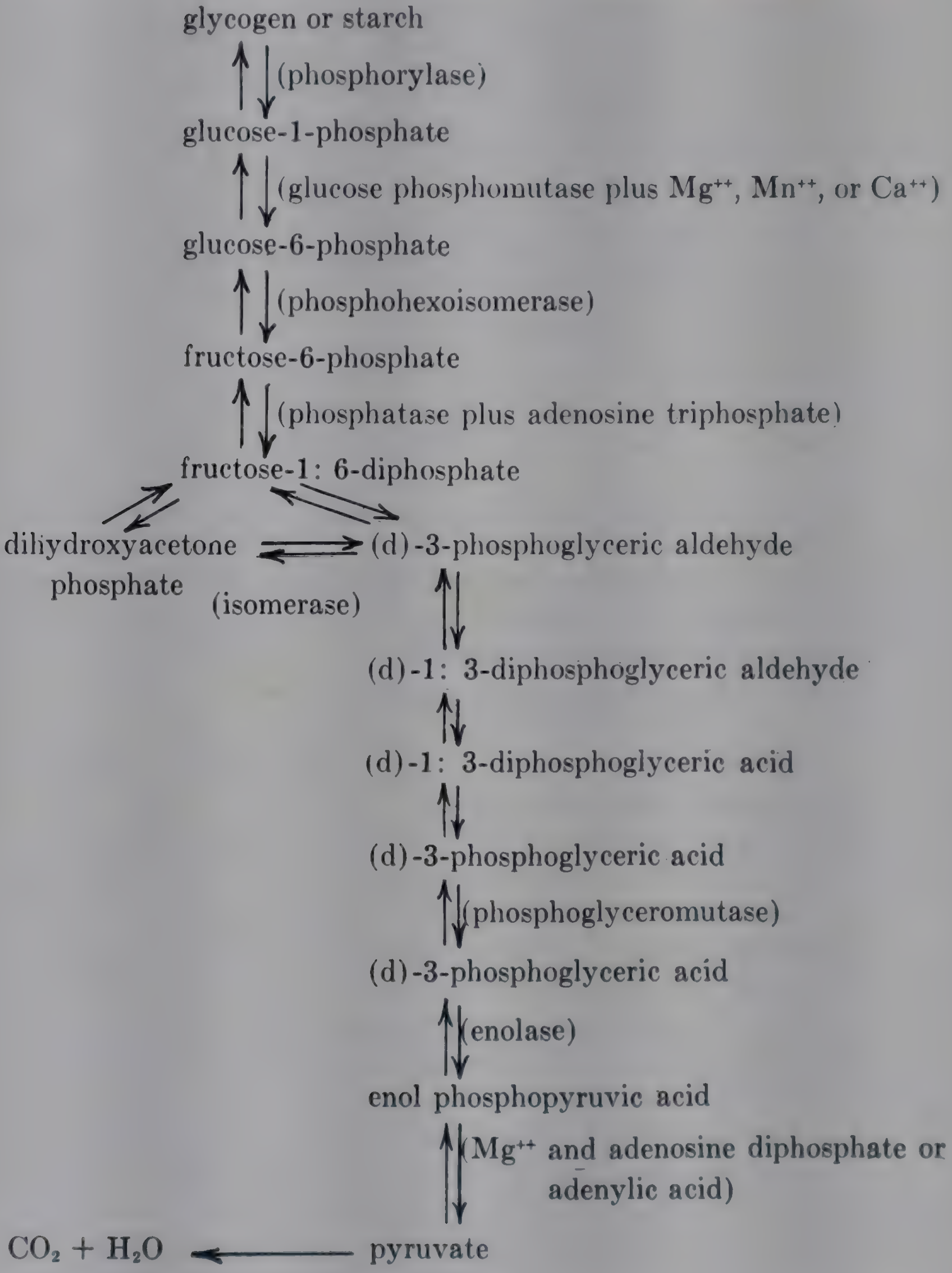
It can be seen from the reactions written above how water is produced through the oxidation of metabolites containing hydrogen. However, these reactions furnish us no clue regarding carbon dioxide formation. Carbon dioxide is produced through the decarboxylation of carboxyl groups according to the reaction:

$$RCOOH = RH + CO_2$$

Such compounds as pyruvic acid furnish carboxyl groups. After decarboxylation has taken place, the residue in certain cases may go through a complicated series of reactions, known as the "Krebs cycle," whereby new carboxyl groups are produced and then decarboxylated.

At first sight there would appear to be no great similarity between the oxidative mechanisms of higher animals, yeast cells, and bacteria. However, closer investigation shows that these three types of life all possess practically the same enzyme systems and that these systems catalyze many reactions which are identical, no matter whether the host is man or a microorganism. Thus, glycogen and inorganic phosphate undergo one reaction after another until pyruvic acid is formed. This compound is converted by the yeast cell to alcohol and carbon dioxide. It is changed by lactic acid bacteria to lactic acid. Higher animals form lactic acid, provided they are not obtaining enough oxygen from an outside source. If enough oxygen is available, higher animals oxidize pyruvic acid to carbon dioxide and water. Lactic acid formation, spoken of as glycolysis, is reversible and lactic acid is readily converted into glycogen.

The reactions which occur when organisms break down glycogen or starch to carbon dioxide and water are shown below:


glycogen or starch
(phosphorylase)
glucose-1-phosphate
(glucose phosphomutase plus Mg⁺⁺, Mn⁺⁺, or Ca⁺⁺)
glucose-6-phosphate
(phosphohexoisomerase)
fructose-6-phosphate
(phosphatase plus adenosine triphosphate)
fructose-1: 6-diphosphate
dihydroxyacetone phosphate
(isomerase)
(d)-3-phosphoglyceric aldehyde
(d)-1: 3-diphosphoglyceric aldehyde
(d)-1: 3-diphosphoglyceric acid
(d)-3-phosphoglyceric acid
(phosphoglyceromutase)
(d)-3-phosphoglyceric acid
(enolase)
enol phosphopyruvic acid
(Mg⁺⁺ and adenosine diphosphate or adenylic acid)
CO₂ + H₂O
pyruvate

In order to synthesize glycogen from glucose it is necessary that the 6-phosphate be formed first. This reaction is brought about by the enzyme known as hexokinase in the presence of adenosine triphosphate. The latter compound supplies the necessary energy as well as the necessary phosphate (p. 486).

The energy which is liberated during glycolysis and by oxidation is stored by living cells in the form of certain compounds of phosphorus which are spoken of as "power phosphates." Some of these are phosphocreatine, adenosine triphosphate, and phospoenol pyruvate. When the organism requires energy for muscular contraction, for absorption, for secretion, or for the synthesis of some compound, these power phosphates lose some or all of their phosphate and furnish the required energy. Later, they are reformed. (See also pp. 486 and 563.)

Under anaerobic conditions pyruvic acid may be reduced to lactic acid. In the yeast cell pyruvic acid is decarboxylated by the enzyme carboxylase, as shown in the following reaction:

$$CH_3COCOOH = CH_3CHO + CO_2.$$

The acetaldehyde thus formed is reduced to ethyl alcohol:

$$CH_3CHO + 2H = CH_3CH_2OH.$$

One of the most interesting of the recent discoveries in enzyme chemistry has disclosed the connection between oxidizing enzymes and vitamins. Unlike the plant, the animal is not always able to synthesize the nonprotein components (coenzymes) of certain oxidizing enzymes. Accordingly these must be supplied in the diet and formed from certain vitamins. Vitamin B_1, or thiamine, after phosphorylation in the cells, is identical with cocarboxylase, which unites with a specific protein to form the enzyme carboxylase. Riboflavin, a component of the vitamin-B complex, is employed by animals to manufacture some twelve or more yellow enzymes, so called because they possess a yellow color (diaphorase, old yellow enzyme, xanthine oxidase, etc.). Another component of the vitamin-B complex, nicotinic acid amide, is needed for the synthesis of codehydrase I and codehydrase II. These two coenzymes can unite with some forty specific proteins to produce oxidizing enzymes.

Chapter X

THE REGULATION OF RESPIRATION; RESPIRATION IN BIRDS

THE REGULATION OF RESPIRATION

THE Respiratory Center. The numerous respiratory muscles—some inspiratory, some expiratory—belong to the skeletal group. They function rhythmically and harmoniously in producing the movements of respiration. The perfect co-ordination, under normal conditions, of so many muscles indicates the existence of a supreme nervous regulating mechanism, a respiratory center. Such a center has been located experimentally in the brain-stem. Section of the spinal cord just below the origin of the phrenic nerves paralyses the intercostal and abdominal muscles but does not interfere with the action of the diaphragm. Section of the cord just below the medulla oblongata paralyzes the intercostal and abdominal muscles and the diaphragm, and the animal dies of asphyxia. Section of the brain-stem above the medulla causes little change in the respiratory movements. Evidently the respiratory center lies somewhere between the upper and lower limits of the medulla oblongata. Many workers have attempted to find the exact location of the group or groups of nerve cells constituting the center or centers.

The recent experiments of Pitts, Magoun, and Ranson (see also Pitts, 1946) are an important contribution to our knowledge of the location, components, and interrelations of the respiratory centers. They explored the medulla of the cat by means of stimulating electrodes inserted into the medullary substance at numerous places. The tests of response to stimulation were changes in the respiratory movements. Numerous points were found from which inspiratory responses could be obtained. Likewise many points were located which gave expiratory responses. The inspiratory center of the cat—as judged by the respiratory responses to stimulation—is located in the ventral reticular formation of the medulla just over the anterior four-fifths of the posterior olive. The expiratory center is located in a region of the dorsal reticular formation dorsal to, slightly anterior to, and cupped over the anterior end of, the inspiratory center. The centers are bilaterally situated in the medulla, but there are connections between the halves across the midline. Each half of the center is in connection with the respiratory motor neurons on both sides of the spinal cord. Thus co-ordinate contraction of the respiratory muscles on the two sides of the body can occur. Using external landmarks to define the limits of the center, one finds that it underlies the posterior third of the floor of the fourth ventricle from the posterior borders of the auditory tubercles to the obex (Pitts). It is estimated that each part (inspiratory, expiratory) of the center of the cat occupies some 30 to 50 cu. mm. of the reticular formation.

It may be pointed out that the studies just mentioned and other modern work do not support the old view that the respiratory center is a sharply localized structure; it is rather diffusely scattered in the reticular formation. Nevertheless there are abundant interneuronal connections between the different parts of each center and between the two centers. The connections within a center are excitatory, enabling a large number of respiratory muscles on both sides of the body to contract. The connections between the centers are inhibitory, providing for central inhibition of the expiratory muscles while the inspiratory muscles are contracting, and the opposite, namely, inhibition of the inspiratory muscles while the expiratory ones are contracting. In eupneic breathing most of the expiratory muscles are inactive (p. 200).

Axons of the neurons of the respiratory center transmit nerve impulses to the motor neurons of the numerous muscles concerned in respiration.

The location of the respiratory center in the cat is similar to its location in the dog as determined by the work of Gesell, Bricker, and Magee, and the same generalization apparently holds for primates.

Rhythmic Activity of the Respiratory Center. The nerve cells that make up the respiratory center show two kinds of rhythmic activity. One has to do with the repetitive discharge, or firing, of individual neurons. The other is concerned with the rhythmic changes in the frequency of firing which produce rhythmic breathing.

The Repetitive Discharge of Nerve Impulses. The nerve cells of the respiratory center, like all cells, are affected by their chemical environment. However, the cells of the respiratory center show a special sensitivity to the partial pressure of carbon dioxide in the arterial blood reaching them. When this pressure rises the nerve cells respond by sending out nerve impulses at a greater frequency. Other changes in arterial blood that are thought to affect the nerve cells of the respiratory center are hydrogen ion concentration, oxygen partial pressure, temperature, and rate of flow. As well as being affected by their chemical environment, the cells of the respiratory center, like other nerve cells, are stimulated by nerve impulses reaching them from various sources. Thus nerve impulses from many parts of the body, including levels of the central nervous system above the medulla, reach and excite the neurons of the respiratory center. As a result of all of these stimuli, chemical and nervous, the neurons of the respiratory center fire repetitively. If the stimulus is increased, the frequency of firing of individual cells is increased and more cells are recruited, or brought into activity. In the normal regulation of respiration, the operation of this mechanism is believed to account for changes in the depth of respiration.

The Genesis of Rhythmic Breathing. According to one view, rhythmic breathing is a manifestation of an inherent *automaticity* of the neurons of the respiratory center. When the center is freed from the influence of all afferent nerve impulses, it continues to send out rhythmic bursts of nerve impulses to the respiratory muscles because of some basic ability which it possesses of discharging rhythmically. According to another view, the rhythm of respiration is imposed upon the respiratory center by inhibitory influences arising from mechanisms outside the center. One of these is the vagal inhibitory mechanism, the other a pontile inhibitory mechanism known as the pneumotaxic center. The latter point of view is the one which appears to have more in its favor at the present time (Pitts).

The Vagal Control of Respiration. The afferent nerve that has the most striking effect on the respiratory center is the vagus. Alternate expansion and collapse of the lungs stimulate mechanically nerve endings (visceroceptors) located in the depths of the lungs (in the walls of the respiratory bronchioles, alveolar ducts, atria, alveolar sacs, and alveoli), and the nerve impulses so generated are transmitted to the respiratory center via the vagi. These impulses accelerate the rate of breathing, decrease the amplitude of breathing, and, in co-operation with nerve impulses descending from the pneumotaxic center in the pons to the respiratory center in the medulla, convert the repetitive discharges of the respiratory center into rhythmic breathing.

Inflation of the lungs stimulates *inflation receptors* in the lungs. These are of two kinds. (1) Moderate inflation of the lungs in eupnea stimulates receptors which give rise to nerve impulses that stimulate the expiratory center and inhibit the inspiratory center. Since in ordinary breathing expiration is mainly passive, the principal effect of these impulses is to inhibit the inspiratory center. In hyperpnea these receptors are stimulated to a greater extent. This general reflex has been designated as an *inspiratory-inhibitory reflex.* (2) In the marked inflation of the lungs seen in hyperpnea, a second type of inflation receptor is stimulated. This gives rise to nerve impulses which stimulate the inspiratory center, thus providing additional muscular contraction for the deep inspiration. This has been designated as an *inspiratory-excitatory reflex.* This reflex probably is unimportant in eupnea.

Deflation of the lungs in hyperpnea stimulates *deflation receptors* which give rise to nerve impulses that stimulate the next inspiration earlier and more powerfully than would occur if the receptors were not present. These receptors are not stimulated in eupnea. This reflex may be designated as an *inspiratory reflex.*

These reflexes were first studied by Hering and Breuer, in 1868, and they are usually designated as *Hering-Breuer reflexes.* They have been extensively studied in recent years by a number of investigators who used modern electrical devices to detect the tiny potential changes that accompany the passage of the nerve impulses.

Abolition of the Hering-Breuer reflexes is readily accomplished by vagotomy. Transection of one vagus usually results in slowing and deepening of respirations. Transection of both vagi causes the response to be more pronounced. Prolongation of the inspiratory phase of respiration accounts for most of the slowing. Deepening of respiration is explained by the prolongation of the discharge of nerve impulses from the inspiratory center to the respiratory muscles, the greater frequency of discharge of the individual neurons, and the recruitment of additional neurons. The deepening of inspiration and the slowing of breathing therefore result from cutting off the inspiratory-inhibitory impulses from the lungs.

Effects of Stimulation of the Central End of a Vagus Nerve on Respiration. The vagi contain not only the afferent nerve fibers concerned in the Hering-Breuer reflexes but also other afferent fibers that can affect the respiratory center, for example, fibers from pressure receptors in the aorta and from chemoreceptors in the aortic bodies. Consequently stimulation of the central end of a vagus nerve will give results that depend on the fibers that are predominantly stimulated. In general, however, stimuli of low intensity and low frequency tend to increase the rate and depth of respiration, whereas stimuli of high intensity and high frequency tend to inhibit respiration in the expiratory phase (Pitts).

The Pneumotaxic Center. Rhythmic breathing is largely the result of the periodic inhibition of inspiration by afferent vagal impulses arising in receptors stimulated by expansion of the lungs. However an animal will continue to breathe rhythmically, although more slowly and more deeply, even after both vagi are transected. Some additional mechanism must be capable of causing rhythmic respirations after the vagal drive has been removed. One view that has been widely held is that the neurons of the respiratory center possess a fundamental automaticity whereby they discharge rhythmically repeated trains of impulses to the respiratory muscles. The other view, which now appears to have more in its favor, is that an inhibitory center exists in the pons capable of periodically inhibiting the respiratory center and producing expiration. This center was designated by Lumsden as the *pneumotaxic center*. It is a bilateral center. During inspiration impulses pass from the inspiratory center to the pneumotaxic center. This in turn sends impulses to the inspiratory center which is inhibited. The decline in activity of the inspiratory center is followed by expiration. Presently the inspiratory center regains its activity and inspiration occurs. The pneumotaxic mechanism is similar to the vagal mechanism in its inhibitory effect on inspiration. When the vagi are cut, rhythmic breathing continues, more slowly and more deeply, under the influence of the pneumotaxic center. When the latter is separated from the medulla in the vagotomized animal, rhythmic breathing stops in the stage of deep inspiration. When the pneumotaxic center is separated from the medulla in an animal with intact vagus, breathing continues in an essentially normal fashion. But when the vagi are cut, rhythmic breathing stops in deep inspiration.

In eupneic breathing the vagal inhibitory mechanism is of more importance, the pneumotaxic mechanism being subsidiary. When the body temperature rises, however, the pneumotaxic center becomes dominant and rapid breathing (polypnea), little affected by bilateral vagal transection, occurs. (In birds, however, bilateral vagotomy abolishes panting—p. 250.) It is believed that impulses from the heat center in the hypothalamus lower the threshold of the pneumotaxic center and cause it to respond more fully to impulses from the inspiratory center.

Chemical Control of Respiration. Changes in the chemical composition of arterial blood influence the respiratory center in two ways. (1) The cells of the respiratory center respond directly to changes in the chemical composition of the arterial blood reaching them. (2) The aortic and carotid bodies contain chemoreceptors which respond to certain chemical changes in their environment, arterial blood.

Direct Chemical Control of the Respiratory Center. Among the possible stimuli that have been the subject of discussion and experiment are the partial pressure of carbon dioxide in the arterial blood reaching the respiratory center, the hydrogen ion concentration of the blood, and the hydrogen ion concentration of the cells of the respiratory center itself (Gesell, 1925). In recent years the last-mentioned theory was the most widely accepted. It appeared very logical and in keeping with a good deal of evidence, admittedly indirect, to relate the chemical stimulus of the respiratory center to the acid products (carbon dioxide, lactic acid) of its own metabolism. But now the balance of evidence (Schmidt and Comroe, 1941; Krogh, 1941; Schmidt, 1945), based on new work, points again to an earlier theory that carbon dioxide in the blood is the chemical stimulus of the center. Apparently the center responds much more vigorously to changes in the partial pressure of carbon dioxide in the blood than to changes in the hydrogen ion concentration of the blood.

Respiratory Chemoreflexes from the Carotid and Aortic Bodies. The carotid and aortic bodies are cell groups or nodules situated in close association with, respectively, the carotid arteries near their bifurcation and the aortic arch. They contain receptors (chemoreceptors, chemoceptors) which respond to certain chemical changes in their environment, arterial blood. The nerve fibers from receptors in the carotid bodies pass to the central nervous system in the sinus nerve, which is a branch of the glossopharyngeal (p. 126). The nerve fibers from the aortic body reach the central nervous system in the vagi. The chemoreceptors in the aortic and carotid bodies function similarly. When activity of the receptors is increased, the respiratory center is stimulated. The centers in the medulla concerned in the regulation of the circulation are also stimulated during increased activity of the chemoreceptors of the aortic and carotid bodies (p. 187).

Much work has been done on the nature of the stimulus to the chemoreceptors. There is general agreement that the following three chemical factors are capable of stimulating them (Schmidt and Comroe; Schmidt, 1945): anoxemia, increase in the partial pressure of carbon dioxide in the blood (hypercapnia), decrease in pH. There is evidence that the most important function of the chemoreceptors in the regulation of respiration is to bring about the hyperpnea that accompanies anoxemia. In anoxemia the chemoreceptors are stimulated and send nerve impulses to the respiratory center increasing its activity. Thus the partial pressure of oxygen in the alveolar air would be increased. In normal human subjects the hyperpnea of anoxia is not marked even at altitudes of 15,000 feet, but at higher altitudes the hyperpnea quickly becomes more pronounced (Schmidt, 1945).

As to the other two factors, hypercapnia and decrease in pH, there is evidence that the receptors are so insensitive to them that their effect in the regulation of respiration via the carotid and aortic bodies is, in ordinary breathing, unimportant. So far as hypercapnia is concerned, the respiratory center is much more responsive to it than are the chemoreceptors. However, under unusual conditions in which the *p*H of the blood falls or hypercapnia develops, effective stimulation of the chemoreceptors may occur.

Additional Nervous Factors in the Control of Respiration. Two important reflex effects on respiration have already been discussed, namely, the Hering-Breuer vagal reflexes and the chemoreflexes from the aortic and carotid bodies. It now remains to consider the following additional nervous factors in the regulation of respiration: respiratory reflexes from the carotid sinus and aorta, respiratory reflexes of a protective nature, the hyperpnea of muscular exercise, and the voluntary control of breathing.

Respiratory Reflexes from the Carotid Sinus and Aorta. The effect of pressure receptors situated in the wall of the carotid sinus and the aorta in the regulation of the circulation is discussed elsewhere (p. 125). The same receptors are of some importance in the regulation of respiration. When stimulated (by an increase of blood pressure in their corresponding arteries), they cause a reflex inhibition of respiration. It is believed that these receptors discharge nerve impulses at low frequencies when the blood pressure is at ordinary levels. A fall in blood pressure causes hyperpnea, due principally to a cessation of inhibitory impulses normally passing to the respiratory center from these receptors. The question of the importance of the pressure receptors in the regulation of respiration in the normal organism is unsettled. The chemoreceptors are thought to be more important than the pressure receptors.

Respiratory Reflexes of a Protective Nature. Stimulation of afferent fibers in many nerves affects the depth and frequency of the respirations. Stimulation of nerve fibers with receptors in the skin, in lightly anesthetized animals, causes an increase in both depth and rate of breathing. It is believed that the fibers causing this response are identical with certain types of pain fibers. The hyperpnea, and the rise of blood pressure that usually accompanies the stimulation, would in the unanesthetized animals be useful in the "fight or flight" responses.

A number of respiratory reflexes take place from the upper air passages. The mucous membranes of the pharynx, larynx, and trachea are supplied with sensation by the glossopharyngeal, anterior laryngeal, and recurrent nerves, respectively. The nasal mucous membrane is supplied with sensation by the trigeminal nerve. Stimulation of the mucous membrane in these regions, or stimulation of the nerves that supply the mucous membrane, causes reflex inhibition of respiration, usually in the expiratory position. A striking example of this is seen in the inhibition of respiration that occurs during swallowing. This inhibition is brought about normally by afferent fibers in the glossopharyngeal nerve. A special example is seen in diving birds and mammals; submergence of the head under water causes reflex inhibition of breathing. Stimulation of the mucous membrane of the larynx in the unanesthetized animal not only causes inhibition of respiration but, usually, also powerful expiratory efforts (coughing). Similarly, stimulation of the nasal mucous membrane in the unanesthetized animal frequently leads to sneezing. Obviously the purpose of all these reflexes is to protect the delicate respiratory passages and the depths of the lungs from harmful substances (irritating gases, dust, food particles) that otherwise might be inspired. To make the protection more certain, the glottis is closed and the bronchi may be constricted.

The Hyperpnea of Muscular Exercise. It is well known that muscular exercise leads to hyperpnea with a consequent increase in the total pulmonary ventilation. It used to be thought that an increase in the chemical stimulus of the respiratory center, brought about by the increased metabolism accompanying the muscular effort, was the cause of the hyperpnea. But recent experiments show that the hyperpnea is often very much greater than can be accounted for by the increase of any identifiable chemical stimulus (carbon dioxide, *p*H) in the blood. In one group of experiments on men the maximum ventilation that could be obtained by inhalation of carbon dioxide was 50 to 60 liters per minute, whereas during exercise these subjects could attain a pulmonary ventilation of twice that amount. Recent work, summarized by Comroe, indicates quite strongly that reflexes acting on the respiratory center are more important in the hyperpnea of exercise than are chemical stimuli acting either directly on the center or on the chemoreceptors. An important source of afferent stimuli in exercise may be the limbs themselves. Experiments suggest that receptors in joints may be concerned in this reflex. Other possible factors operating in the hyperpnea of exercise are *p*H changes affecting the chemoreceptors or the respiratory center, adrenaline release, elevation of temperature, a rise of venous pressure in the great veins and right atrium, and motor discharges from the higher brain centers.

The rate of pulmonary ventilation does not fall to its resting level as soon as muscular work subsides. It continues at a higher level for a time, only gradually returning to normal. The time required for the return depends on the amount of muscular exercise taken and the condition of the subject; where the work performed is light and the subject is in good training the return is rapid. The lag in the return of the pulmonary ventilation to the resting level indicates that the metabolic rate of the organism remains at a higher level for a time following the exercise.

Voluntary Control of Breathing. Ordinarily respirations proceed quite involuntarily. However, it is a matter of everyday experience that they may be altered within wide limits voluntarily; they may be hastened, slowed, or stopped altogether, for a while. If respirations are entirely inhibited voluntarily, that is, if the breath is held, there soon comes a time when the individual must breathe again; the cells of the respiratory center escape from the inhibition.

Phonation and related acts, and the use of the abdominal press in the expulsive acts of defecation, urination, and parturition, are all examples of more or less complete voluntary control of the respiratory (chiefly expiratory) movements. These acts, however, are not concerned in the gaseous exchange between the organism and its environment but are secondary uses to which the respiratory apparatus may be put.

Definite areas have been located in the cerebral cortex whose electrical stimulation causes excitatory and inhibitory alterations in the respiratory movements. In this way the respiratory center can be brought under the control of the cortex (Smith).

Some Respiratory Reflexes in the Pig, Sheep, and Goat. A limited number of observations on respiratory reflexes in the pig have been reported by Dukes and Schwarte. The anesthetic used was urethane or ether. Tightly tying (crushing) the vagus nerves gave inconstant results on respiration. No general conclusion could be drawn. Stimulation of the central end of the vagus nerve gave as the prevailing response complete inhibition of respiration; this was especially true for the left nerve. But other responses were common. Stimulation of the central end of the sciatic nerve gave many kinds of responses. Negative results were not uncommon. Occlusion of both carotid arteries caused little or no effect on breathing. A response to stimulation of the central end of a vagus nerve in the pig is shown in Fig. 70.

Some observations on respiratory reflexes in sheep have been made by Rangsit. Tightly tying the left vagus nerve usually caused slower and deeper respirations. Weak stimulation of the central end of the vagus nerve often produced a cough reflex. Strong stimulation usually caused inhibition of breathing. Stimulation of the central end of the sciatic nerve gave inconstant results on respiration. Burlage has reported a few observations on the nervous control of respiration in the sheep. A response to stimulation of the central end of a vagus nerve on respiration in a sheep is shown in Fig. 71.

A marked postural polypnea in goats kept at ordinary room temperature in the dorsal recumbent position have been observed by Greenberg, Petersen, and Visscher. Exposing the polypneic animals to a cold environment caused a prompt decrease in the respiratory rate.

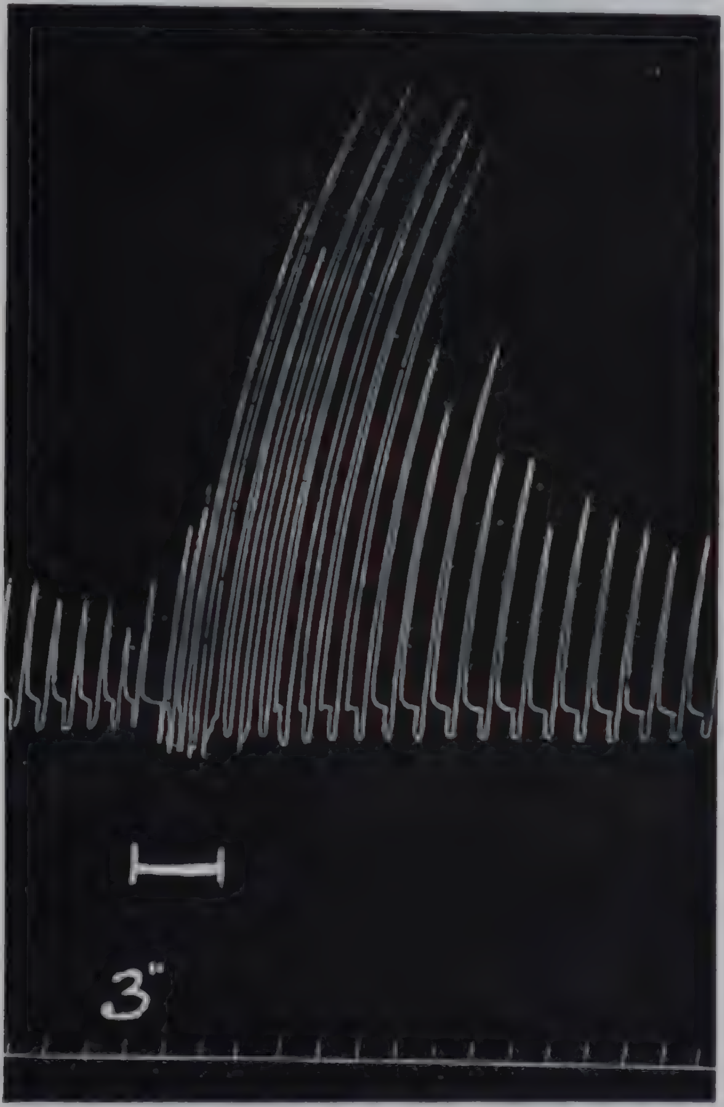


FIG. 70.—Effect of stimulation of central end of vagus nerve on respiration (pig). The downstroke indicates inspiration. I—I indicates the duration of the stimulus.

The Onset of Respiration at Birth. The lungs of the fetus are, so far as gaseous exchange is concerned, nonfunctional. After birth they take over this function. Although the fetus does not breathe through the lungs, it nevertheless makes respiratory movements in the uterus. This has been shown to be true in a number of species (Snyder and Rosenfeld). The respiratory center of the fetus cannot therefore be regarded as being in a state of apnea, as used to be thought. The former belief, that the respiratory center is apneic, arose from the fact that the observations had been made on anesthetized animals, in which fetal breathing movements are usually absent.

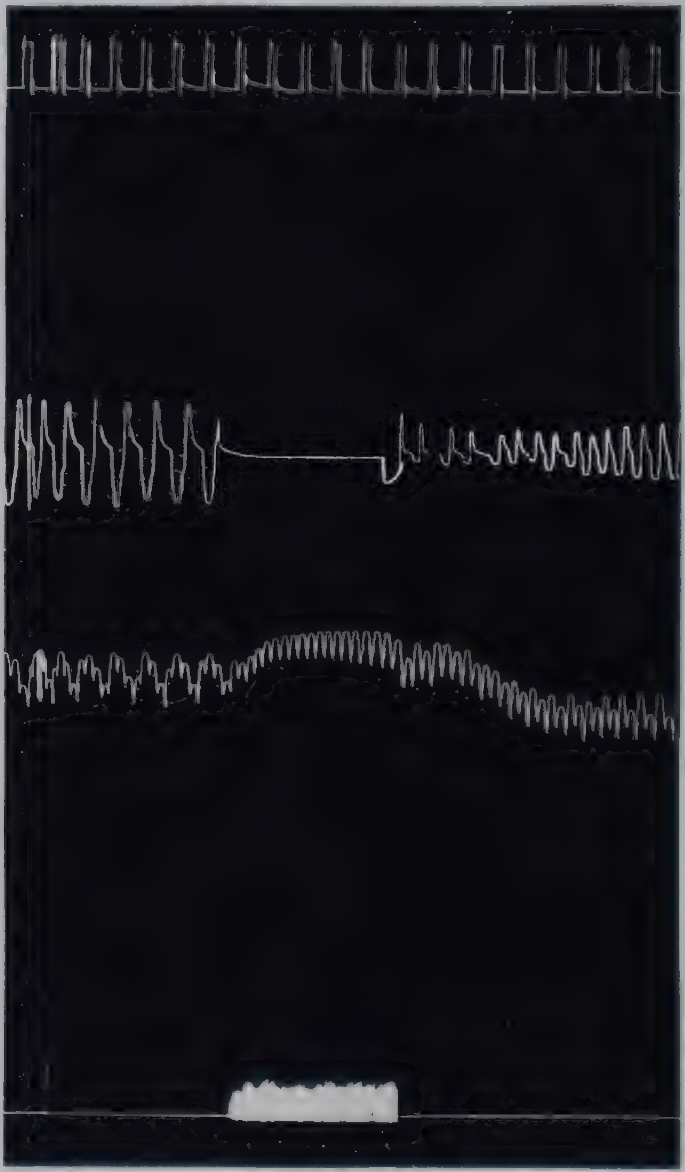


FIG. 71.—Effect of stimulation of central end of right vagus on respiration (above) and blood pressure of a sheep. Coil distance, 5 cm. Downstroke indicates inspiration. The time tracing indicates intervals of 2 sec. Chloral hydrate and ether anesthesia. (Rangsit.)

During birth fetal respiratory movements are diminished or abolished, so that the newborn animal is in a state of apnea. The question arises as to what starts the respiratory movements again. It is probable that factors of importance are the hypercapnia and anoxia that develop following failure of the placental circulation. Thermal and tactile stimuli from the skin as well as proprioceptive stimuli from the now active limbs probably help. However, the precise nature of the stimulus that starts respirations after birth is unknown.

RESPIRATION IN BIRDS

The lungs of birds are small. They are situated in the dorsal part of the thoracic cavity and adhere rather firmly to its wall. Several of the ribs make deep impressions in the lungs. The structure of the lungs is different from that of mammals. Alveoli in the ordinary sense are absent, the air apparently coming, by way of the air capillaries, into direct contact with the endothelium of the pulmonary blood capillaries. The bronchial system is quite different from that of mammals. Certain of the large bronchi pass through the lungs to terminate in the air sacs.

These mucoserous sacs may be regarded as continuations of the bronchi beyond the lungs. Nine air sacs are recognized. The terminology differs among different investigators. Following is the classification of McLeod and Wagers: thoracocervical, anterior thoracic, posterior thoracic, lesser abdominal, greater abdominal. All of the air sacs are paired except the anterior thoracic. The walls of the air sacs are thin and have a poor blood supply. It is believed that no significant amount of gaseous exchange occurs through their walls.

Arising mainly from the abdominal air sacs, but also to some extent from the others, are the recurrent bronchi. They penetrate the lung parenchyma and anastomose with the main bronchial system. Air passing to the greater abdominal sacs apparently undergoes but little gaseous exchange on its way through the lungs. Air going to the other air sacs is submitted to a variable degree of gaseous exchange on its way through the lungs. There is thus some gaseous exchange in the bird during inspiration. However, analysis of the gases of the air sacs and observations of the distribution of radiopaque dust in the airways indicate that most of the gaseous exchange occurs on expiration during the passage of the air from the air sacs through the recurrent bronchi into the lung substance (Graham), where they anastomose with the main bronchial system.

The data given in the table on p. 250 show the composition of air in the various air sacs of the fowl. It will be noted that the air in the abdominal (greater abdominal) sacs resembles most closely atmospheric air in composition. This indicates that air passing to these sacs undergoes the least gaseous exchange in the lungs on its way to the sacs.

The composition of expired air of the fowl is as follows: oxygen, 13.5 volumes per cent; carbon dioxide, 6.5.

During inspiration in the bird the thoracic and abdominal cavities are enlarged, with the result that air is drawn into the lungs and air sacs.

Composition of Air Obtained from Air Sacs at End of Inspiration

Air Sac	Abdominal (Greater Abdominal)	Posterior Thoracic (Lesser Abdominal)	Anterior Thoracic (Posterior Thoracic)	Inter-clavicular (Anterior Thoracic)	Cervical (Thoraco-cervical)
	vol. per cent	*vol. per cent*	*vol. per cent*	*vol. per cent*	*vol. per cent*
O_2.....	19	17.4	16.3	14.6	15.6
CO_2...	2	3.4	3.2	5	3.2

The terminology of McLeod and Wagers is shown in parentheses.

According to McLeod and Wagers, the chicken possesses two diaphragms. The thoraco-abdominal diaphragm is a thin, tendinous sheet separating the thorax and abdomen. The pulmonary diaphragm is a horizontal sheet dividing the thorax into upper and lower parts.

Some Respiratory Reflexes in the Fowl. These have been studied by Graham. Following are some of the conclusions reached by this worker. Transection of the vagi in the neck slows breathing, after an initial stimulation. Slower breathing and an increase of respiratory tonus result from stimulation of the central end of one vagus with weak shocks, the other vagus being intact. Inflation of an isolated lung and its air sacs promotes expiration. Deflation of the lung is without effect on respiration. The fowl shows the Hering-Breuer reflex, its chief action being to promote expiration. Ordinarily expiration lasts twice as long as inspiration. Section of one vagus nerve in the bird has no effect on panting, but bilateral vagotomy abolishes panting at once. Bilateral vagotomy in mammals does not abolish panting. The significance of afferent vagal fibers (from inflation receptors in the lungs) in the regulation of respiration is greater in birds than in mammals (Hiestand and Randall, 1942).

The effects of carbon dioxide inhalation on respiration in many species of birds have been studied. Variations in the responses were obtained. In some species stimulation of breathing results. In others there is an inhibitory effect producing partial or complete cessation of breathing. The inhibitory effect of carbon dioxide on respiration results from stimulation of receptors in the nasopharynx (Hiestand and Randall, 1941).

As compared with mammals, little has been done on the physiology of respiration in the fowl. Many problems, especially with respect to the gaseous exchange and the significance of the air sacs, remain unsolved.

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PART IV

Digestion and Absorption

Chapter XI

DIGESTION: INTRODUCTORY CONSIDERATIONS

THE term digestion is used here in a broad sense to include all activities of the alimentary tract and its glands in the preparation of foods for absorption and in the rejection of the residue. Most foods are consumed in too complex and insoluble a form to be absorbed into the blood or lymph without preliminary digestive changes. Glucose, soluble salts, water, and a few other foods require no digestion. The majority of foods, however, must undergo more or less elaborate changes prior to absorption.

The factors of digestion are mechanical, secretory, chemical, and microbiological. The chief mechanical factors are mastication, deglutition, regurgitation, vomiting, gastric and intestinal motility, and defecation. The secretory factors are the activities, or work, of the digestive glands. The chemical factors are enzymes, both those produced by the digestive glands and the less important plant enzymes; and certain nonenzymic chemical substances (for example, hydrochloric acid) produced by the digestive glands. The microbiological factors are bacteria and possibly in some species protozoa.

The relative importance of the different factors of digestion are not known in all instances and for all species. However, some information on these points will develop in the discussions to follow.

FOODS

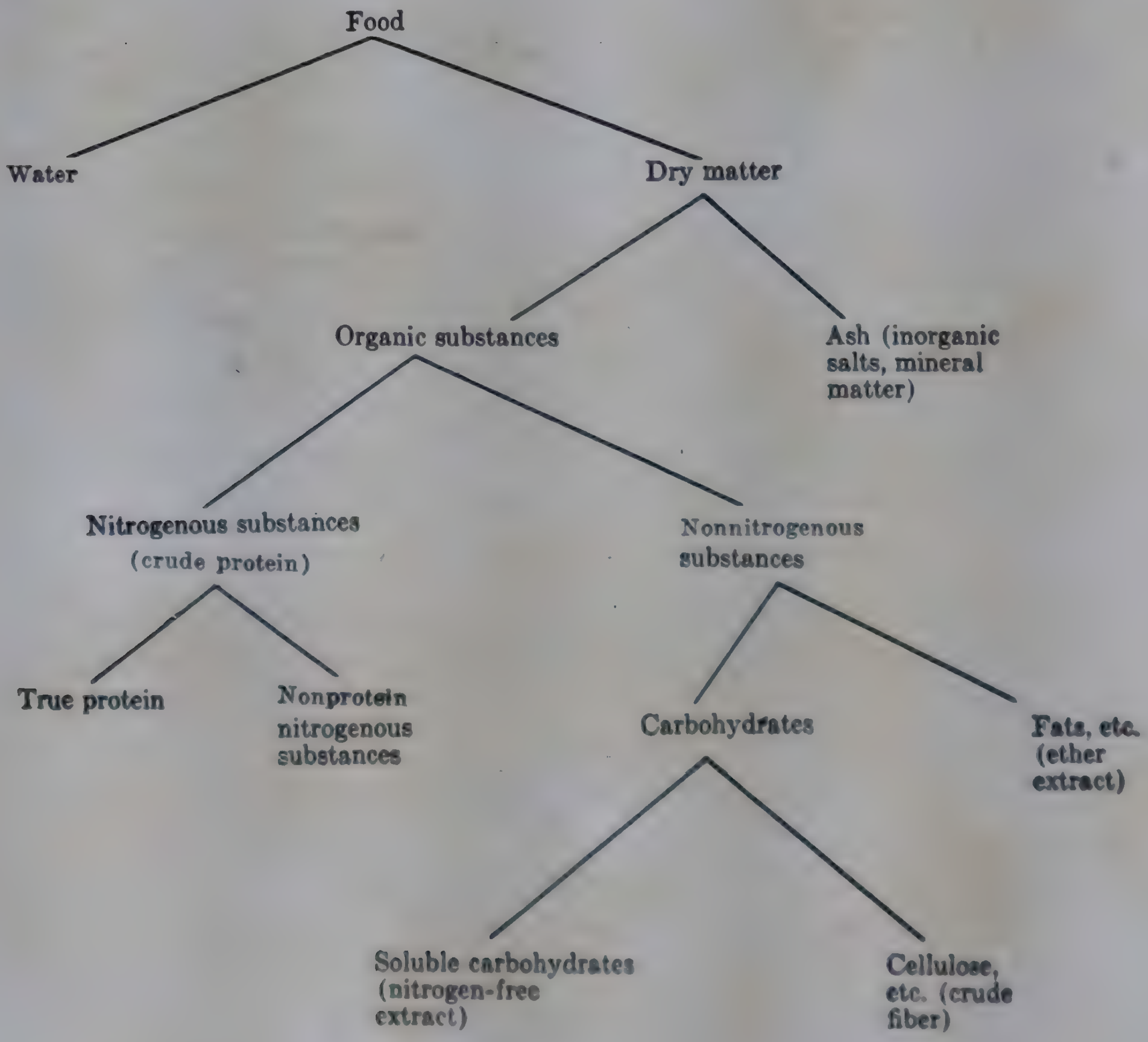
A food is a mixture of foodstuffs. In order to meet the nutritive requirements of an animal the diet must supply at least the following foodstuffs:

Proteins
Carbohydrates
Fats
Inorganic salts
Water
Vitamins

It is the exceptional single food that contains all the foodstuffs in the right quantity and of the right quality. Hence it is usually necessary for the animal to have a variety of foods in order to remain healthy.

Proteins, fats, carbohydrates, and vitamins do not occur in nature except in association with or as a part of living matter. The higher animals are therefore dependent on plants or other animals for these requirements. Some animals, the carnivores, obtain the bulk of their food from animal sources. Among the domestic animals the dog and cat are by nature carnivorous, although man has, for economic reasons, added a good deal of food of vegetable origin to their diet. Certain other animals, the herbivores, obtain their food from vegetable sources. They are represented among domestic animals by the horse, ox, sheep, goat, and rabbit. Still others, the omnivores, consume food of both plant and animal origin. The pig is the domestic representative of this group, although under domestication this animal is largely herbivorous. Man himself is an excellent example of an omnivorous animal.

Composition of Foods. The diagram below (modified from Linton) may be helpful in visualizing the different components of a


Food
Water
Dry matter
Organic substances
Ash (inorganic salts, mineral matter)
Nitrogenous substances (crude protein)
Nonnitrogenous substances
True protein
Nonprotein nitrogenous substances
Carbohydrates
Fats, etc. (ether extract)
Soluble carbohydrates (nitrogen-free extract)
Cellulose, etc. (crude fiber)

food. Vitamins are not included in the diagram. However, a great deal is known about their composition. The table below shows the composition of some of the common vegetable foods fed to domestic animals in this country.

Composition of Common Foods of Domestic Animals
(Henry and Morrison)

Food	Water	Ash	Crude Protein	Fiber	N-free Extract	Fat
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Corn, dent, well dried	10.5	1.5	10.1	2.0	70.9	5.0
Oats	9.2	3.5	12.4	10.9	59.6	4.4
Field pea	9.2	3.4	22.9	5.6	57.8	1.1
Cottonseed meal, choice	7.5	6.2	44.1	8.1	25.0	9.1
Linseed meal, new process	9.6	5.6	36.9	8.7	36.3	2.9
Linseed meal, old process	9.1	5.4	33.9	8.4	35.7	7.5
Wheat bran	10.1	6.3	16.0	9.5	53.7	4.4
Timothy hay	11.6	4.9	6.2	29.8	45.0	2.5
Alfalfa hay	8.6	8.6	14.9	28.3	37.3	2.3
Red clover hay	12.9	7.1	12.8	25.5	38.7	3.1
Cowpea hay	9.7	11.9	19.3	22.5	34.0	2.6
Oat straw	11.5	5.4	3.6	36.3	40.8	2.4
Corn fodder, fresh, green	78.1	1.2	1.9	5.2	13.0	0.6
Kentucky bluegrass, fresh, green	68.4	2.8	4.1	8.7	14.8	1.2
Alfalfa, green	74.7	2.4	4.5	7.0	10.4	1.0
Turnip	90.5	0.9	1.4	1.1	5.9	0.2
Rape	83.3	2.2	2.9	2.6	8.4	0.6
Corn silage	73.7	1.7	2.1	6.3	15.4	0.8

ENZYMES OF THE ALIMENTARY TRACT

Most of the chemical changes occurring in the digestive processes are brought about by the action of enzymes. These may be defined as organic catalysts produced by living matter. Each of the enzymes so far isolated has been found to be a protein. A convenient list of the principal enzymes of the alimentary canal is given in the accompanying table.

THE ALIMENTARY TRACT

The alimentary tract extends from the lips to the anus. The parts are: mouth, pharynx, esophagus, stomach, and small and large intestine. As regards complexity and length, the tract varies greatly in

PRINCIPAL ENZYMES OF THE ALIMENTARY TRACT

Enzyme	Where Mainly Found	Substrate	End-Products
Ptyalin (salivary amylase)	Saliva	Starch	Dextrins, maltose
Pepsin (gastric protease)	Gastric juice	Proteins	Proteoses, peptones
Rennin	Gastric juice	Casein	Paracasein
Gastric lipase	Gastric juice	Fats	Higher fatty acids, glycerol
Trypsin (pancreatic protease)	Pancreatic juice	Proteins, proteoses, peptones, peptides	Peptones, peptides, amino acids
Amylopsin (pancreatic amylase)	Pancreatic juice	Starch, dextrins	Dextrins, maltose
Steapsin (pancreatic lipase)	Pancreatic juice	Fats	Higher fatty acids, glycerol
Carboxypeptidase	Pancreatic juice	Peptides containing free carboxyl group	Amino acids
Several peptidases (old name, erepsin)	Small intestine	Peptides	Amino acids
Sucrase (invertase)	Small intestine	Sucrose	Glucose, fructose
Maltase	Small intestine	Maltose	Glucose
Lactase	Small intestine	Lactose	Glucose, galactose
Polynucleotidase	Small intestine	Nucleic acid	Purine and pyrimidine nucleotides
Nucleotidase	Small intestine	Purine nucleotides	Purine nucleosides, phosphoric acid

different species. In carnivores it is short and relatively simple, whereas in herbivores it is comparatively much longer and more complex. In some herbivores (horse, rabbit) the stomach is relatively simple and is comparable to that of carnivores, whereas the large intestine is much more complex and voluminous than that of carnivores. In certain other herbivores, the ruminants, the stomach is extremely large and complex, whereas the large intestine, though long, is of relatively small caliber. The accompanying tables illustrate some of the statements just given. The first table shows the relative and absolute lengths of the different parts of the intestine and the ratio of length

LENGTH OF DIFFERENT PARTS OF THE INTESTINE (ADAPTED FROM COLIN)

Animal	Part of Intestine	Relative Length	Average Absolute Length	Ratio of Body Length to Length of Intestine
		per cent	*meters*	
Horse	Small intestine	75	22.44	1:12
	Cecum	4	1.00	
	Large colon	11	3.39	
	Small colon	10	3.08	
	Total	100	29.91	
Ox	Small intestine	81	46.00	1:20
	Cecum	2	0.88	
	Colon	17	10.18	
	Total	100	57.06	
Sheep and goat	Small intestine	80	26.20	1:27
	Cecum	1	0.36	
	Colon	19	6.17	
	Total	100	32.73	
Pig	Small intestine	78	18.29	1:14
	Cecum	1	0.23	
	Colon	21	4.99	
	Total	100	23.51	
Dog	Small intestine	85	4.14	1:6
	Cecum	2	0.08	
	Colon	13	0.60	
	Total	100	4.82	
Cat	Small intestine	83	1.72	1:4
	Large intestine	17	0.35	
	Total	100	2.07	
Rabbit	Small intestine	61	3.56	1:10
	Cecum	11	0.61	
	Colon	28	1.65	
	Total	100	5.82	

CAPACITY OF DIFFERENT PARTS OF THE GASTRO-INTESTINAL CANAL
(ADAPTED FROM COLIN)

Animal	Part of Canal	Relative Capacity	Average Absolute Capacity
		per cent	*liters*
Horse	Stomach	8.5	17.96
	Small intestine	30.2	63.82
	Cecum	15.9	33.54
	Large colon	38.4	81.25
	Small colon and rectum	7.0	14.77
	Total	100.0	211.34
Ox	Stomach	70.8	252.5
	Small intestine	18.5	66.0
	Cecum	2.8	9.9
	Colon and rectum	7.9	28.0
	Total	100.0	356.4
Sheep and goat	Rumen	52.9	23.4
	Reticulum	4.5	2.0
	Omasum	2.0	0.9
	Abomasum	7.5	3.3
	Small intestine	20.4	9.0
	Cecum	2.3	1.0
	Colon and rectum	10.4	4.6
	Total	100.0	44.2
Pig	Stomach	29.2	8.00
	Small intestine	33.5	9.20
	Cecum	5.6	1.55
	Colon and rectum	31.7	8.70
	Total	100.0	27.45
Dog	Stomach	62.3	4.33
	Small intestine	23.3	1.62
	Cecum	1.3	0.09
	Colon and rectum	13.1	0.91
	Total	100.0	6.95
Cat	Stomach	69.5	0.341
	Small intestine	14.6	0.114
	Large intestine	15.9	0.124
	Total	100.0	0.579

of body to length of intestine; the second shows the relative and the absolute capacities of the stomach and the different parts of the intestine. All measurements were made at autopsy.

Lengths of intestine determined at autopsy probably do not represent the lengths as they occur in the living animals. Alvarez (1928) has pointed out the difficulty, even the fallacy, attending the measuring of intestinal lengths in dead subjects. Espe and Cannon (1940) made measurements of the length of the intestine in living calves (5 to 12 months old) and in the same calves at autopsy. In vivo the average length of small and large intestine combined was 28 feet 7 inches. At autopsy the average combined length was three times as great.

Chapter XII

PREHENSION, MASTICATION, SALIVARY SECRETION, DEGLUTITION

PREHENSION OF FOOD

As applied to digestion, the term prehension means the seizing and conveying of food to the mouth. The methods used by different animals vary greatly. In bipeds the upper limbs are the principal prehensile organs, whereas in most quadrupeds they are unimportant in this respect. Clawed animals hold their prey with their front limbs but do not use them to carry food to the mouth. In all domestic animals the lips, teeth, and tongue are the principal organs of prehension. The relative importance of these is not the same in all species.

In the dog and cat the food is often held with the fore limbs, as indicated above, but it is passed into the mouth largely by head and jaw movements.

In the horse the upper lip is the main prehensile structure. For this purpose it is sensitive, strong, and mobile. In grazing the action of the lip places the food between the incisor teeth by which the food is then cut off. In manger feeding the loose food is collected by the lips with the aid of the tongue.

In the ox the chief organ of prehension is the tongue. The lips, owing to their limited power of movement, are not prehensile. The tongue, long, strong, mobile, and rough, is capable of being protruded from the mouth and can readily be curved around grass, which is then drawn between the incisor teeth below and the dental pad above and cut off.

The sheep has a cleft upper lip, which, though not prehensile, permits very close grazing. The incisor teeth and the tongue are the principal prehensile structures, but the tongue is not protruded in grazing as in the ox. The upper lip of the goat is not cleft.

Under natural conditions the pig digs up the ground with the snout and carries the food so obtained to the mouth largely by the action of the pointed lower lip. When pigs are not permitted to root, prehension is accomplished by the teeth, tongue, and characteristic movements of the head.

Drinking and Sucking. The way in which liquids are carried to the mouth varies greatly in carnivores and herbivores. The dog and the cat make a ladle of the free end of the tongue by which liquid is carried to the mouth. The other domestic animals draw liquid into the mouth by suction, the lips being closed all around except for a small place in front, which is under water. The tongue is the structure chiefly concerned in producing the necessary negative pressure in the mouth; its action is comparable to the piston of a pump.

Sucking is accomplished by creating negative pressure in the mouth, largely by the action of the tongue. Milk in the teat is subjected to pressure somewhat higher than atmospheric; hence it is forced into the mouth, where the pressure, because of the action of the tongue, is lower than that of the atmopshere. Negative pressures of great magnitude are developed during sucking by calves (Smith and Petersen).

MASTICATION

Mastication or chewing is the mechanical reduction of food that takes place in the mouth. It is between the molar teeth that the grinding occurs. The importance of mastication lies in the fact (1) that finely divided food presents a greater surface than coarse food for the action of the digestive juices and (2) that food well mixed with saliva is more easily swallowed. Mastication, however, is not of the same importance in all species. In carnivores it is very imperfectly performed, whereas in herbivores, owing to the coarse, bulky nature of the food, it is of much greater significance. In ruminants, however, it is only during remastication that food is thoroughly ground. Omnivores occupy a position between carnivores and herbivores.

The principal movement of the lower jaw that any animal can make is a movement in a vertical plane. In carnivores this is by far the most important jaw movement. In herbivores, on the other hand, the power of lateral movement is well developed, and there is also some to-and-fro movement. In harmony with the kind of food naturally consumed and the nature of the jaw movements, the teeth of different animals show remarkable differences in size, shape, and structure. In carnivores and omnivores, where movements in a vertical plane suffice, the upper and lower jaws are of equal width, and the teeth are relatively simple; there is no necessity for an elaborate grinding apparatus. In herbivores simple up-and-down movements of the mandible are inadequate to crush and grind the tough, coarse food. Therefore provision must be made for lateral movements in order to insure adequate reduction of the food between the molar teeth. Because of this, the upper jaw is wider than the lower, and mastication can occur on only one side at a time. Furthermore, owing to this lateral or "crossed" movement of the lower jaw, the molar teeth wear with chisel-shaped grinding surfaces. The sharp edge of the lower teeth is innermost, while that of the upper teeth is outermost. At times these edges may become sharp enough to damage the tongue or the cheek, respectively. The oblique tables of the teeth of herbivores are composed of substances of different degrees of hardness; hence these surfaces wear rough. This roughness increases the grinding efficiency. The hard, elevated areas are composed of enamel.

The incisor teeth are not grinding structures. As their name implies, they are used to detach and cut or lacerate food. In ruminants the upper incisors are absent and the lower ones loose and obliquely placed in their sockets in order to prevent injury to the dental pad above.

The mandible is provided with two kinds of muscles: those that close the mouth and those that open it. The former are much more powerful. Of the muscles that close the jaws, the temporals are most highly developed in carnivores, the masseters in herbivores.

Herbivores spend a great deal of time masticating, and the number of jaw movements is large. Colin determined that it requires a horse one and a fourth hours for the mastication of four pounds of dry hay, out of which 60 to 65 boluses are made. The rate of mastication varies from 70 to 80 strokes per minute. Fuller observed that dairy cows make an average of 94 jaw movements per minute when eating grain and silage and 78 per minute when eating hay. This worker then calculated that a dairy cow makes approximately 4700 jaw movements daily while eating grain and silage, and 10,530 while eating hay. In addition to the jaw movements during eating, there are something like 26,400 during rumination. Thus there is a total of some 42,000 jaw movements daily in dairy cows. This means of course that in these animals an enormous amount of energy is expended in mastication.

Depending on the ration eaten, steers spend 1.4 to 11 per cent of the daily time in mastication (Kick and co-workers).

Aside from the purely masticatory movements, there are concomitant tongue and cheek movements by which the food is kept between the molar teeth and gradually worked backward for swallowing.

Mastication is an act under the control of the will; it may be started or stopped or the rate may be altered voluntarily. Nevertheless, as usually performed, the muscles involved are stimulated to action entirely reflexly. The normal stimulus is the presence of food in the mouth.

Grazing habits of cattle have been studied by Atkeson, Shaw, and Cave and by Johnstone-Wallace and Kennedy.

THE SALIVARY GLANDS AND THEIR SECRETION

The term salivary glands refers to the three main salivary glands, all of which are paired, and the numerous small glands found in the mucous membrane of the mouth. Saliva is the mixed secretion of all these glands. The three main glands are the parotid, submaxillary (mandibular), and sublingual.

Glands in general may be divided into serous, mucous, and mixed types. Serous glands give rise to a thin, watery secretion containing protein but no mucin; mucous glands produce a secretion containing the glycoprotein mucin; mixed glands partake of the nature of both serous and mucous glands.

Cells that give rise to a serous secretion frequently also produce enzymes, which are discharged as a part of the secretion. So-called zymogen granules, presumably the precursors of enzyme, are found stored in the serous cells. Mucous cells do not produce enzymes, according to the general belief.

The parotid glands of most mammals are serous. However, in some animals the secretion of the glands is devoid of enzyme. The fact, then, that a gland yields a serous secretion does not necessarily mean that it is an enzyme producer. The submaxillary gland is mixed in some species, serous in others. In man, ungulates, the dog, and the cat it is mixed; in rodents it is serous. The sublingual gland of the horse, ox, pig, dog, and cat is a mixed gland; that of rodents is mucous.

Nerve Supply of the Salivary Glands. The salivary glands receive a double efferent innervation. One set of nerves is derived from the parasympathetic division of the autonomic system, the other from the sympathetic division. The sympathetic fibers for all three glands leave the spinal cord as preganglionic fibers in the ventral roots of the first two or three thoracic nerves and pass up the cervical sympathetic chain to the anterior cervical ganglion, where they terminate synaptically around nerve cells from which new fibers arise. These postganglionic fibers run to the salivary glands in the walls of the arteries supplying the glands. The parasympathetic preganglionic fibers to the parotid gland leave the brain-stem by the glossopharyngeal nerve, pass through the tympanic plexus to the trigeminal nerve, and thence by its auriculotemporal branch to the gland. The synaptic junctions are located in the otic ganglion. The parasympathetic preganglionic fibers to the submaxillary and sublingual glands leave the brain-stem by the facial nerve, run in its chorda tympani branch to join the lingual nerve (branch of the trigeminal), and leave this to enter the glands. The synaptic junctions are in the submaxillary ganglion, which is in the glands themselves.

The afferent fibers of the salivary secretory centers are contained chiefly in the trigeminal and glossopharyngeal nerves. These nerves conduct impulses of taste and general sensibility from the mouth. The salivary centers are susceptible also to impulses reaching them by other nerves.

The nuclei, or centers, for salivary secretion are located in the medulla oblongata. Chatfield explored the medulla of the cat with stimulating electrodes that could be manipulated with a stereotaxic apparatus. It was found that secretion could be evoked by stimulation of a number of points in the medulla. "These points lay mostly in the reticular formation and in the region of the intramedullary course of the facial or glossopharyngeal nerves." In general, the points whose stimulation gave predominantly submaxillary secretion were located "rostral and medial to the middle third of the facial nucleus." These points are believed to represent the submaxillary center. Points whose stimulation gave parotid secretion "were concentrated caudal to and above the submaxillary center, and medial to and above the cranial end of the nucleus ambiguus."

Stimulation of the Nerves of the Salivary Glands; the Secretory Process. In view of the fact that the chief experiments on the nervous regulation of salivary secretion have been made on the submaxillary gland of the dog, the results of stimulation now to be outlined relate principally to the condition in this gland and species. Moreover, because important experiments bearing on the problem of secretion in general have been made on the submaxillary gland, it is advisable to study briefly the results of such experiments. However, one is not justified in saying without proof that the results of experiments made on the submaxillary gland are applicable to other glands.

Electrical stimulation of the peripheral end of the chorda tympani causes a copious secretion of submaxillary saliva, which can readily be collected by inserting a cannula into the gland duct. The amount of saliva secreted varies, within limits, with the intensity of stimulation. When the stimulus is removed the secretion diminishes and finally ceases. Accompanying the secretion is a marked vasodilatation in the gland, the blood flow being increased five to eight times. Stimulation of the peripheral (cephalic) end of the cervical sympathetic nerve causes the secretion of a small amount of thick saliva containing much mucin. (In the cat sympathetic stimulation causes a copious, watery secretion from the submaxillary gland.) In addition, since the sympathetic nerve carries constrictor fibers to the blood vessels of the head, there is a marked vasoconstriction in the salivary glands during sympathetic stimulation.

Stimulation of the sympathetic fibers to the parotid gland causes no evident secretion of saliva, but that an effect on the gland cells occurs is indicated by the observation that parasympathetic stimulation during or following sympathetic stimulation results in a saliva rich in organic matter. Ordinary stimulation of the parasympathetic nerves to the parotid gland causes a copious flow of watery saliva.

Recent evidence indicates that the parasympathetic effects on the salivary glands are caused by the liberation of acetylcholine at the nerve terminations, and that the sympathetic effects are brought about by the liberation of an adrenalinelike substance (sympathin). The similar findings with respect to the cardiac and other autonomic nerves may be recalled at this time.

A number of *drugs* effect the peripheral salivary secretory mechanism. They have been valuable in studies on the innervation and the secretory process. Atropine paralyzes the parasympathetic effects. Following its injection chorda stimulation causes no secretion of saliva although vasodilatation still takes place. Pilocarpine (Fig. 72), arecoline, acetylcholine, and other substances stimulate the parasympathetic terminations and cause a copious flow of saliva. Adrenaline stimulates the sympathetic terminations.

Saliva, like all secretions, is formed of course ultimately from the blood; but the question arises here, as with other glands, whether the formation is a true secretory act, the ultimate chemistry and physics of which are unknown, or an act dependent merely on known physical or physicochemical processes such as filtration, osmosis, and diffusion. That saliva is *secreted* by the gland cells, that is, that the gland cells play an active part in its formation and do not constitute merely a membrane across which filtration, diffusion, and similar processes go on, is indicated by a number of observations such as the following: (1) It was shown by Ludwig years ago, and has been confirmed by many others since, that the submaxillary gland can secrete against a pressure that is greater than the blood pressure in the carotid artery. The submaxillary duct is cannulated and connected to a mercury manometer. The cartoid artery is also cannulated and connected to a manometer. The chorda tympani is stimulated: the salivary secretion pressure rises considerably and may exceed the blood pressure. (2) During secretion of saliva the gland consumes increased amounts of oxygen and blood sugar, produces an increased amount of carbon dioxide, and gives other evidence of metabolic change (Deutsch and

Raper, Northup). (3) The gland elaborates substances not present as such in the blood, for example, mucin. Clearly, then, it is necessary to look beyond the physicochemical laws as at present understood for an explanation of the process of secretion. When new laws are discovered, or when the old laws receive further interpretation, it may be that a physicochemical explanation will be forthcoming. Stimulat-

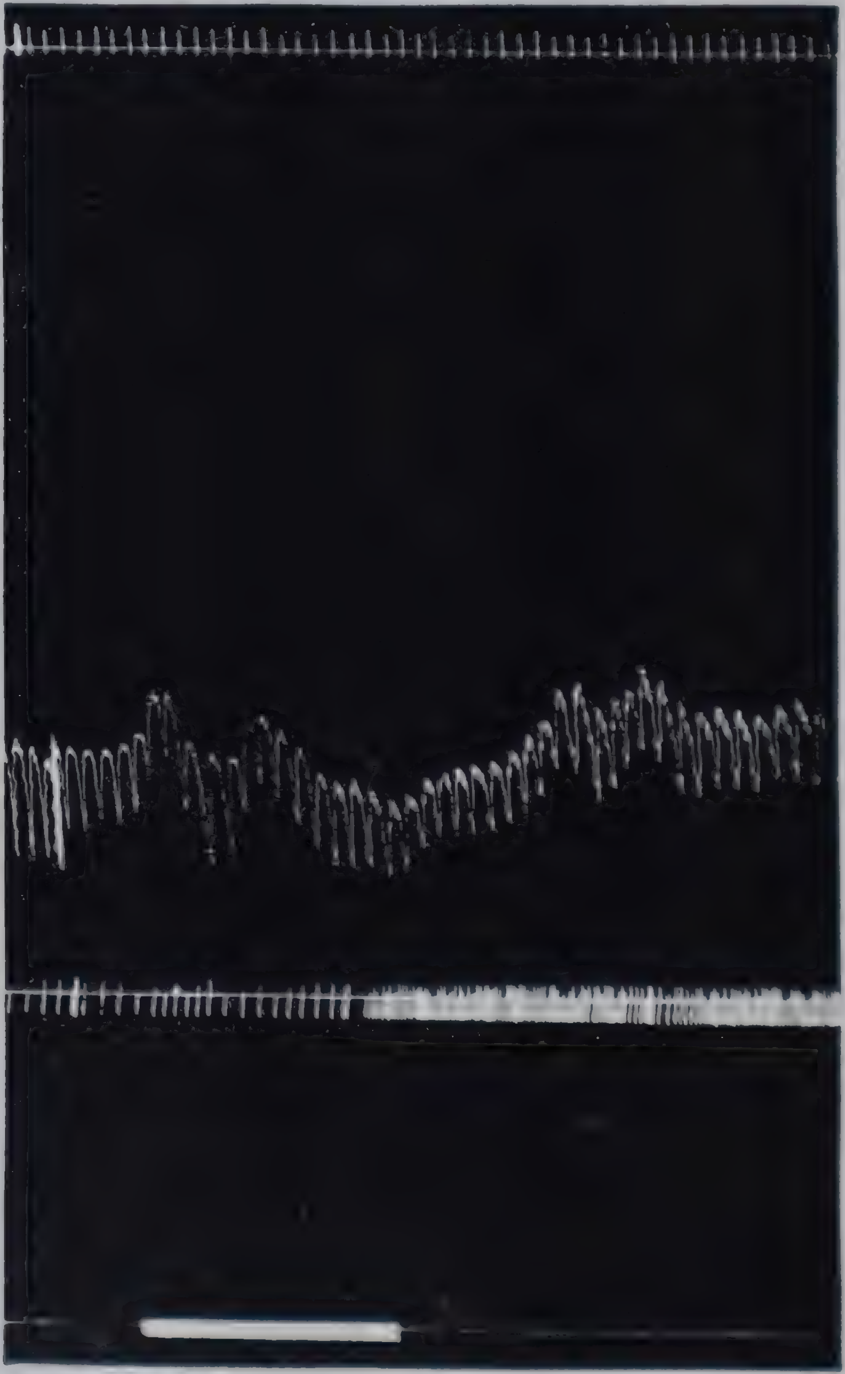


Fig. 72.—Effect of pilocarpine on blood pressure and parotid salivary secretion of a sheep. Chloral hydrate and ether anesthesia. Tracings (from top to bottom): time, 3 sec.; carotid blood pressure; drops of saliva from a cannula in a parotid duct; base line. At the signal on the base line, 10 mg. of pilocarpine hydrochloride were injected intravenously. (Rangsit.)

ing hypotheses have been advanced in an effort to explain secretion in terms of physics and chemistry. Bayliss' book may be consulted in this connection. See also the review by Höber.

Some glands, in addition to being regulated by the nervous system through secretory nerves, have also a control by chemical stimuli brought to the gland by the blood (humoral control). Still other glands have the humoral control only. So far the salivary glands have not been shown to come under humoral control (Ivy, 1930). However, as indicated above, neurohumoral agents (acetylcholine, sympathin) are concerned in salivary secretion.

The Normal Regulation of Salivary Secretion. The secretion of saliva is a complex reflex act involving receptors, afferent nerves, secretory centers, efferent secretory and vasomotor nerves, blood vessels, and gland cells. Two general methods of exciting this secretory mechanism are available to the organism.

1. It is a familiar fact that food does not have to enter the mouth in order to cause a flow of saliva. The sight or odor or even the thought of food, provided the individual is hungry, calls forth salivary secretion; the mouth is said to water. This reflex has been studied extensively in dogs. The afferent paths are in the optic and olfactory nerves; the connections in the cerebrum are complex. Because the reflex involves the cerebrum it is sometimes designated a *psychic* reflex. Psychic secretion appears to be slight (Seymour) or absent (Scheunert and Trautmann) in the horse and absent in the sheep (Scheunert, Krzywanek, and Zimmermann). It is probable that it is small or absent in all herbivores. It has been demonstrated in the pig (Trautmann).

The nature of the saliva secreted as a result of the psychic reflex varies with the character of the food. Thus Pavlov, who made a detailed study of the psychic salivary reflex in the dog, has shown that the sight of meat calls forth a stringy saliva from the submaxillary and sublingual glands but none from the parotid, whereas the sight of dry meat powder or dry bread calls forth an abundant secretion of parotid (thin) saliva. Evidently the effect of the saliva secreted in the first instance is, when the meat enters the mouth, to lubricate the morsel for swallowing, whereas in the second instance it is to moisten the dry food preparatory to swallowing.

Pavlov termed psychic reflexes *conditioned* reflexes because they are dependent, for their formation and maintenance, upon a number of conditions or circumstances. They are the acquired reflexes in contrast with the inherited reflexes. Pavlov found that neutral stimuli added to the natural or unconditioned stimulus become effective after a number of repetitions. Thus if, when a dog is fed, a certain sound is made, for example, a bell is rung, and this association of sound and food is repeated frequently, a time will come when the sound alone will be effective in causing saliva to flow. For a fuller discussion of conditioned reflexes, see Chapter XXXIV.

2. When food enters the mouth a much more copious secretion of saliva is called forth. This is because of reflex stimulation of the salivary centers by the action of the food on receptors of taste and of general sensibility. Here again the quality and especially the quantity of the saliva are adapted to the character of the food. Thus the chewing of meat causes a free flow of submaxillary and sublingual saliva but none from the parotid, whereas dry meat powder excites an abundant parotid secretion. Fresh moist bread causes little or no secretion; dry bread, a copious flow. As Pavlov states, the role of saliva is, above everything else, that of a watery secretion. This is especially true in herbivores, whose food is so often of a dry nature. In this connection Claude Bernard noted years ago that it was with the greatest difficulty that a horse swallowed dry food, such as oats and hay, when deprived only of its parotid secretion. Thorough mastication means of course increased salivary secretion because the food remains in contact with the sensory nerve endings in the mouth for a longer time.

In the horse chemical stimuli (taste) play but little part in parotid secretion; the stimulus is chiefly due to the mechanical action of the food on the buccal mucous membrane. In this same animal parotid saliva shows no chemical adaptation to the food (Scheunert and Trautmann). The parotid secretion of the horse is not continuous but occurs only when the animal is eating food. The secretion is largely unilateral, the amount produced on the side of mastication being several times greater than on the other side. When the side of mastication shifts, the secretory activity of the parotids also shifts.

In ruminants parotid secretion is continuous. This insures adequate moisture and alkali for the functioning of the first three stomach compartments. In the sheep parotid secretion is only slightly increased as a result of feeding, and not at all during rumination. The mandibular glands of this animal secrete during the taking of food but not during rumination nor in the intervals between feeding (Scheunert and Trautmann). The mandibular glands of the ox also are practically quiescent during rumination.

Amount of Saliva. The amount of saliva secreted has been investigated in a number of animals. Enormous in herbivores, the quantity is greater in the ox than in the horse. Colin estimated the amount secreted in the following way: An esophageal fistula was made in the neck of the animal to which a weighed amount of food was given; the mastication time was noted; the food was collected as it fell from the fistula. The food was again weighed and from this weight was subtracted the original weight. The difference represented the amount of saliva secreted during the eating period. In this way Colin found that a small horse eating hay secreted 5000 gm. (about 5000 cc.) of saliva in an hour, a medium-sized horse 5200 gm., and a large horse 8800 gm. When oats were eaten the amount of saliva formed was only two-thirds as much as the amount above; green fodder, half as much; roots, a third as much. Additional experiments show that dried fodder absorbed four times its weight of saliva, oats a little more than their own weight, meal twice its own weight, and green fodders only half their own weight. It is seen that the amount of salivary secretion is inversely related to the amount of moisture in the food. This serves to emphasize the statement already made that saliva functions mainly as a watery secretion.

It is estimated that the horse secretes something like 42,000 gm. (about 10 gallons) of saliva in 24 hours and the ox 56,000 gm. (R. M. Smith). In man the amount is believed to be about 1500 gm.

Composition of Saliva. Saliva from the individual salivary glands may be obtained for study by inserting a cannula into a gland duct (Fig. 73) or by implanting the end of a severed duct into an opening in the skin. Mixed saliva may be obtained from the mouth, as by the use of a sponge, or from a fistula of the esophagus. Mixed saliva is a colorless, viscid, easily frothing, slightly opalescent liquid. The reaction of saliva of man is usually slighly acid. According to Starr, the average reaction is *p*H 6.6. Other investigators have reported similar results. Alkalinity may develop if the saliva is allowed to stand. This is due to loss of carbon dioxide. In the domestic animals, except ruminants, the reaction is slightly alkaline; in ruminants it is distinctly alkaline. Schwarz and Hermann obtained the following mean *p*H values: pig, 7.32; dog and horse, 7.56; ox, 8.1. Schwarte, using a colorimetric method, obtained mean *p*H values as follows: horse, 7.42; ox, 8.23; pig, 7.37; dog and cat 7.5.

The water content of saliva is very high, hence the specific gravity is only slightly greater than 1.0 (horse, sp. gr. 1.005). Saliva contains organic and inorganic constituents in small amounts. The dissolved organic matter in mixed saliva consists mainly of mucin, other proteins, and, in some animals, the enzyme ptyalin. The suspended organic matter consists of desquamated epithelial cells and leucocytes (salivary corpuscles). The inorganic salts are the same in kind as those of the blood. However, the total amount is less than, and the proportion of the different salts is not the same as, in blood. The most abundant salt is sodium chloride. Thiocyanates, often found in the saliva of man and sometimes of the dog, are said to be absent from the saliva of the horse, ox, sheep, goat, and pig.

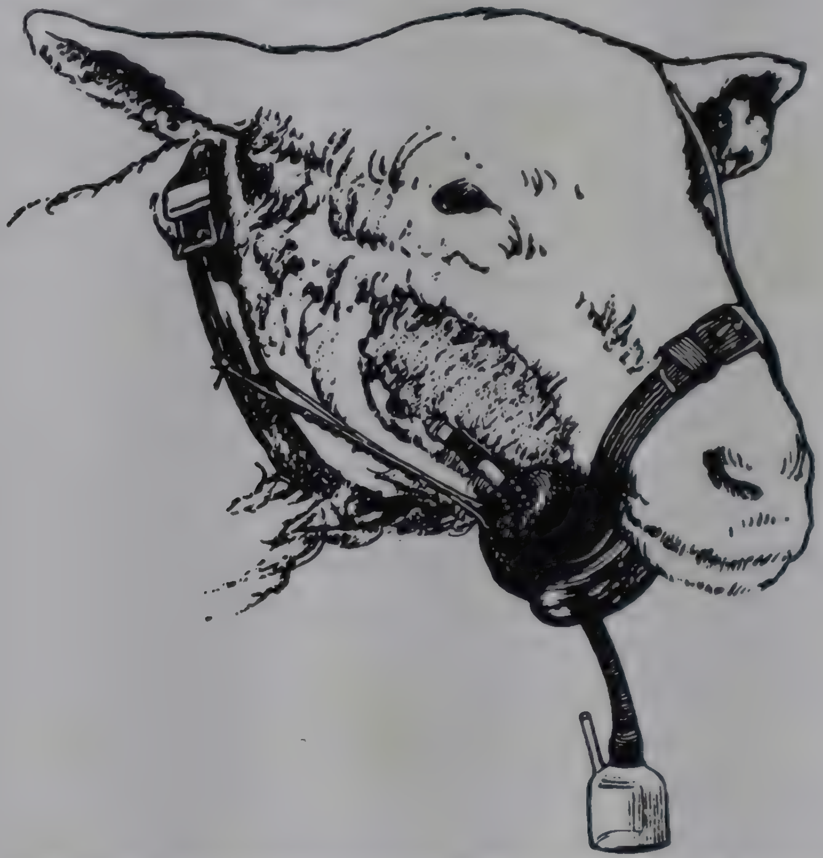


Fig. 73.—A method of collecting saliva from the parotid duct. A cannula has been inserted into the duct. (From Scheunert and Trautmann, Pflüger's *Archiv für die gesamte Physiologie,* 1921, **192**.)

The accompanying table, abstracted from a compilation by Moore (1898), illustrates the composition of saliva in several domestic animals. Additional data for animals may be obtained from a review by Lenkeit (1933).

Functions of Saliva. Saliva functions mainly in a physical way, that is, as a watery secretion. In some animals is has, by virtue of its

Composition of Saliva (parts per 1000)

Saliva	Water	Total Solids	Organic Matter	Inorganic Matter
Parotid of horse......	990	10	2.06–6	4.8–8.73
Submaxillary of cow.	991.14	8.86	3.53	5.33
Sublingual of dog....	986.3	13.7	4.3	9.4
Mixed of dog........	989.6	10.3	3.58	6.79

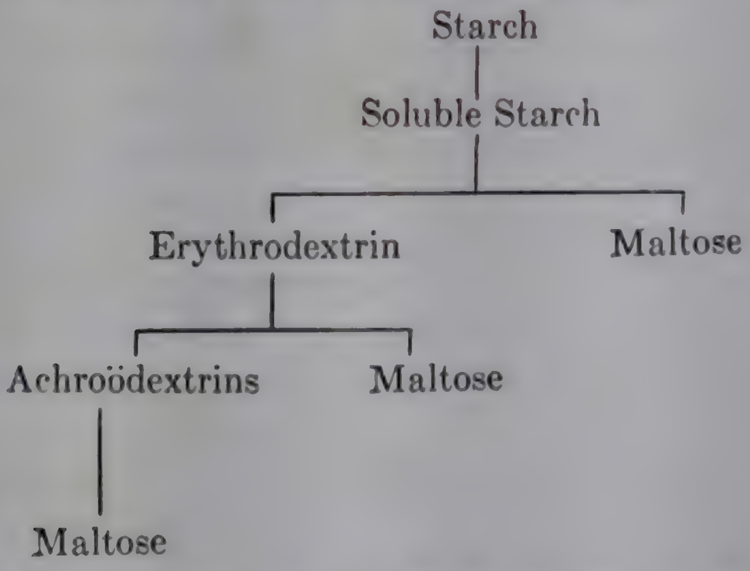
enzyme content, the additional function of converting starch to sugar. The saliva of ruminants, because of its high alkalinity, helps to maintain a proper reaction in the rumen, where organic acids are produced by bacterial fermentation.

Reference has already been made to the usefulness of saliva as a watery secretion. It moistens the food, thus facilitating mastication and swallowing, and dissolves some of the food, thus providing stimulation for the taste receptors. Because of the mucin content of saliva the food particles are easily formed into a bolus for swallowing and the swallowing passages are lubricated.

The saliva of some animals and of man contains an amylolytic enzyme termed ptyalin or salivary amylase. The action of this enzyme is to hydrolyze starch, through a series of dextrins, to maltose. The changes during starch digestion can be followed by the use of iodine solution. The exact steps are not agreed upon; one view is shown in the diagram below.

Starch and soluble starch give a blue color with iodine; erythrodextrin a red color; the achroödextrins, of which there are several, no color. Maltose is a disaccharide and responds to the various copper reduction tests.

One of the factors influencing enzymic action is the hydrogen ion concentration of the medium in which the action takes place. According to Groll the optimum reaction for the activity of human ptyalin is *p*H 6.2. Other investigators place the optimum *p*H somewhat higher than this. The range in which ptyalin will act is wide (*p*H 4-9). The chloride ion enhances the action of salivary amylase.



It has long been recognized that food remains in the mouth too short a time to permit much starch hydrolysis to take place. However, the former belief that the distinct acidity of the gastric juice destroys salivary amylase almost immediately after swallowing is now known to be incorrect. The food mass upon entering the stomach is not at once mixed with the gastric juice, intimate mixing occurring only in the pyloric portion. The food mass in the cardiac extremity is therefore only slowly penetrated by the acid gastric juice, so that in this location salivary digestion can proceed uninterruptedly for a considerable time (man, 15 to 30 minutes—Bergeim). However, in those animals possessing amylase in the saliva, starch digestion is not completed in the stomach. Much of the digestion, especially of the intermediate products, occurs under the action of pancreatic amylase in the intestine.

Maltase, found in small amount in saliva, at least of man, and in ample amount in the small intestine of all species, hydrolyzes maltose to glucose.

Effects of Loss of Saliva. Complete loss of saliva in young pigs through an experimentally produced fistula of the esophagus has been found not to interfere with growth (Wilder and Stokes). Continued loss of parotid saliva in goats is said to result in death unless sodium bicarbonate is given to the animal.

Occurrence of Ptyalin. Considerable differences of opinion have existed as to which animals possess sufficient amounts of salivary amylase to be of significance in digestion. A study of recent literature appears to justify the conclusion that among domestic animals the pig stands alone in possessing a saliva containing enough amylase to be of significance in digestion. Even in this animal the amylolytic power of saliva is much weaker than that of the saliva of man. Some might classify the dog with the pig in this regard, although the evidence hardly justifies it. A summary of some of the literature follows:

Horse. The (mixed) saliva contains no amylase (Carlson and Crittenden; Schwarz and Steinmetzer; Schwarte). Parotid saliva contains no amylase (Scheunert and Trautmann). The salivary glands give off insignificant amounts of amylase (Seymour, Hayden, Finkelstein). The conclusions of Palmer and co-workers that the salivary glands produce an inactive ptyalin, which is activated by orokinase formed by the buccal and possibly the lingual glands, could not be confirmed by Hayden or Finkelstein.

Ox. The saliva contains no amylase (Schwarz and Steinmetzer; Schwarte). The amount present is insignificant (Palmer, Finkelstein).

Sheep. The saliva contains no amylase (Scheunert and Trautmann, Schwarz and Rasp).

Goat. The saliva contains no amylase (Carlson and Crittenden, Schwarz and Rasp, Trautmann and Albrecht).

Pig. The saliva contains an amylase (Schwarte), but the amylolytic action of human saliva is more than a hundred times as powerful as that of pig saliva (Schwarz and Steinmetzer). The parotid saliva of the pig is amylolytic (Trautmann).

Dog. The saliva contains a small amount of amylase of blood origin (Carlson and Ryan, Gayda). Schwarz and Steinmetzer found no amylase in dog's saliva. A "polyamylase" is occasionally present in small amounts (Galehr). Its occurrence appeared to bear no relation to the amount of carbohydrate in the diet. Submaxillary saliva has amylolytic power (Roseboom and Patton).

Cat. The saliva contains a small amount of amylase derived from the blood (Carlson and Ryan). The saliva of the cat has no amylolytic ferment (Schwarz and Rasp).

Fox. Parotid saliva contains a small amount of amylase of blood origin (Carlson and Crittenden).

Rabbit and Guinea Pig. The saliva of the rabbit has a weak amylolytic action, but the possibility that the enzyme is of food origin was not excluded. The saliva of the guinea pig undoubtedly contains an amylase (Schwarz and Rasp).

Starch Digestion by the Dog. There is a rather widespread popular belief that the dog has little or no ability to digest starch. This belief probably arose from the fact that the saliva of the dog contains little or no amylase. However, an abundance of scientific evidence as well as practical experience in the feeding of dogs indicates that the dog can digest and utilize large amounts of starch. McCay points out that if the diet of the dog is otherwise satisfactory there is no reason why it should not contain a large amount (50 to 60 per cent) of starch or other carbohydrates.

Although the dog has little or no salivary amylase, it possesses an abundance of pancreatic amylase and some intestinal amylase.

Pregastric Changes in Milk Drunk by Calves. Experiments by Wise, Miller, and Anderson indicate that milk drunk by calves undergoes modification, apparently of a digestive nature, before it reaches the stomach. The calves were sham-fed by causing the ingested milk to run out of an esophageal fistula or out of a flexible tube inserted into the cardiac orifice via a rumen fistula. Among the changes noted in the sham-fed milk were decrease in *p*H, increase in lipolytic activity, and increase in rate of coagulation by rennin. It is suggested that the salivary or esophageal glands may secrete a lipolytic enzyme.

DEGLUTITION

Deglutition or swallowing is the act of conveying food from the mouth through the pharynx and esophagus to the stomach. It is a complex reflex act involving a great number of muscles and their motor nerves, a deglutition center in the medulla oblongata, and afferent nerves with receptors in the mucous membrane of the posterior part of the mouth and pharynx.

Structure of the Esophagus. In all animals the wall of the esophagus is made up of four layers: a fibrous coat, the muscular coat, the submucosa, and the mucous membrane. The kind of muscle varies somewhat in different species, but in most animals striated muscle is found throughout the esophagus. In the horse the muscle is striated to the base of the heart, where it changes to the smooth type; in the ox, sheep, and dog it is striated throughout; in the pig it is striated throughout, except in the part near the cardia. The rate of passage of swallowed food is faster in the striated than in the smooth part.

In the ox, glands are found in the mucous membrane of the esophagus at its pharyngeal end; in the pig they are numerous in the anterior half of the tube; in the dog they are present throughout.

The Act of Swallowing. For many years it has been customary to divide the act of swallowing into three phases corresponding to the passage of the food (1) from the mouth into the pharynx, (2) through the pharynx into the esophagus, and (3) down the esophagus into the stomach. However, division of the act into such phases is from the physiological standpoint purely arbitrary and for descriptive purposes only. In the following description no definite attempt is made so to divide deglutition.

After undergoing appropriate mastication and insalivation, the food is passed by the tongue to the back of the mouth and thence through the isthmus faucium into and through the pharynx and esophagus. Dry food or food imperfectly moistened is swallowed with difficulty or not at all. Such food does not supply the necessary stimulus which starts the series of muscular contractions involved in swallowing. At the pharynx the respiratory and digestive passages cross. It is therefore necessary that food traverse this region quickly lest accident occur, such as aspirating the food into the larynx or forcing it into the nasal passages. As further insurance against mishap, respiration is completely inhibited, via afferent fibers in the glossopharyngeal nerve, the glottis is closed, and the posterior nares are blocked by elevation of the soft palate.

The muscular force necessary to drive the food through the isthmus faucium and pharynx into the esophagus is derived chiefly from the contraction of the mylohyoid and hyoglossus muscles, although others assist. The former muscle presses the tongue against the hard palate and the latter muscle draws the root of the tongue backward. At the same moment elevation of the soft palate cuts off communication with the nasal passages. The tongue thus acts as a plunger driving the mass of food toward the esophagus. The hyoid bone and the larynx are now pulled forward; thus the entrance into the esophagus is opened. At the same time the epiglottis appears, in some animals, to be pressed over the opening into the larynx until it is shut. It is said that in man the upper half of the epiglottis can be removed without causing trouble but that if the base of the epiglottis is interfered with difficulty in swallowing results (Alvarez, 1940). Anatomical considerations make it doubtful whether in some animals (horse) the epiglottis is folded over the laryngeal aperture at all. The bolus of food now enters the esophagus. The pharyngeal events of swallowing take place with great rapidity and are difficult to analyze in detail.

The manner and rate of passage of the bolus through the esophagus vary in different species, in different parts of the esophagus, and with different consistencies of the food mass. Cannon and Moser have studied this question in a number of animals by means of the roentgen ray and otherwise. Results obtained by the roentgen ray are more trustworthy than those obtained by inserting balloons, stomach tubes, and other devices into the esophagus, as was commonly done before the introduction of the roentgen-ray method. This method has revealed that in some instances the bolus is carried down solely by peristalsis (a traveling ring of constriction in a tubular organ caused by contraction of its muscular coat), whereas in other instances it is rapidly shot into the depths of the esophagus. However, even in the latter instances, a peristaltic movement of local origin passes over the terminal part of the esophagus and sweeps into the stomach the food mass, which does not come to a pause. Cannon and Moser studied deglutition in the goose, cat, dog, horse, and man.

In the goose, food, whether solid or liquid, is carried down the esophagus by peristalsis alone, at an average rate of a little more than a centimeter per second. Shooting of liquid from the mouth down the esophagus, therefore, does not occur in the fowl, for the structures in the mouth are not adapted to this movement. Hence, in the absence of squirting, gravity plays a greater part. Cannon found that when the mylohyoid muscles are paralyzed the mammal raises the head in swallowing and thus relies to a greater extent on gravity. Under these conditions the mammal swallows after the manner of birds.

In the dog and cat solid and semisolid foods pass down by peristalsis alone, whereas liquids are squirted for some distance down the esophagus, to be carried into the stomach by a peristaltic wave. In the cat a bolus requires 9 to 12 seconds to reach the stomach; in the dog, 4 to 5 seconds.

In the horse solid and semisolid foods pass by peristalsis alone, at a rate of 35 to 40 cm. per second. Liquids are squirted down the esophagus, by a contraction of the mylohyoid muscles, at a rate more than five times as great as the rate of solid or mushy foods. It is easy to convince oneself of the essential correctness of these statements for the horse by observing the animal while it is eating or drinking. In the cow and in man the condition is similiar to that in the horse. In quadrupeds during grazing swallowing has to take place largely against gravity.

The Nervous Control. Swallowing is a reflex act. The placing of food into position for the commencement of swallowing is under voluntary control but requires no attention. In the pharyngeal mucous membrane are certain sensory spots which when stimulated cause swallowing. In all animals a chief spot lies in the course of the bolus from mouth to pharynx. In the rabbit it is on the fore part of the soft palate and is innervated by the maxillary branch of the trigeminal nerve. In the dog and cat it is on the dorsal wall of the pharynx and is supplied by the glossopharyngeal nerve. It has been shown that when a local anesthetic is applied to the chief spot swallowing becomes, for a time, difficult or impossible. Less sensitive spots have been mapped out at the lower part of the pharynx, supplied by the anterior and posterior pharyngeal nerves; the dorsal surface of the epiglottis, supplied by the anterior laryngeal nerve; and other places.

The deglutition center is made up of a group of nerve cells located in the floor of the fourth ventricle. It is a correlation center presiding over the motor nuclei of the numerous nerves involved in swallowing. The center is stimulated by afferent impulses from the sensory spots mentioned above. As a result of such stimulation the center discharges a series of impulses to the muscles concerned, additional stimuli from the succeeding parts of the deglutitory canal to the center being unnecessary for the completion of the act. However, peristaltic waves caused by reflex discharges from the swallowing center can arise at any point in the esophagus if a stimulus from the esophagus is present. Those waves caused by discharges from the center when it is stimulated from the pharyngeal region, that is, those waves which run the entire course of the esophagus, are designated as primary waves; those that arise from local stimuli, for example, food remnants, in the esophagus are designated as secondary waves. The former are not interrupted even by complete transection of the esophagus; the latter are dependent on the continuity of the tube. To these types of movement in the esophagus must be added a third type found only where smooth muscle exists—in the terminal part of the esophagus in some animals.

The esophagus is supplied with motor nerve fibers by the vagi. In the thoracic portion the esophageal branches of the vagi supply the tube, in the cervical portion the recurrent nerves, and in the upper cervical part other vagus branches. Sympathetic nerves have been shown to exert some influence over the terminal part of the esophagus. Primary and secondary peristalses of the esophagus are dependent on the integrity of the vagus, whereas peristalsis in the smooth-muscle part is of local origin. This means that this part of the esophagus is largely independent of the nervous system so far as motor activity is concerned, and is therefore automatic. The stomach and intestine also possess a high degree of motor automaticity.

The Cardia. The opening of the esophagus into the stomach, the cardia, is closed by a sphincter of smooth muscle known as the cardiac sphincter. Its degree of development varies in different animals. In the horse it is supposed to be especially well developed and powerful; in ruminants it is not well developed. The function of the sphincter is to inhibit the passage of food from the stomach into the esophagus. Except during swallowing and regurgitation, the cardia is probably ordinarily closed. Cannon held that the closure of the cardia is caused by acidity in the stomach, but later work (Carlson, Boyd, and Pearcy) throws doubt upon this conclusion. The cardiac sphincter is composed of smooth muscle and is therefore doubtless capable of a certain amount of independent or automatic activity, varying with changing conditions on the esophageal and stomach sides. Nevertheless, the muscle is under some degree of control from the central nervous system. Carlson, Boyd, and Pearcy have studied its innervation in the dog, cat, and rabbit. In the cat the vagi and splanchnic (sympathetic) nerves contain both motor and inhibitory fibers for the cardia. In the dog and rabbit stimulation of these nerves gave results that suggested some differences from the condition in the cat, but it is possible that the variations obtained were due to the degree of tonus of the sphincter at the time of stimulation. The activity of the motor and inhibitory nerve fibers of the cardiac sphincter is probably controlled reflexly.

Chapter XIII

DIGESTION IN THE SIMPLE STOMACH

AFTER the food is swallowed it is received by the stomach, where it is submitted to the various factors that collectively constitute gastric digestion. The relative complexity of stomach digestion varies considerably in different animals, depending upon the structure and functions of the stomach and the kind of food naturally consumed by the animal.

As regards stomach structure and function, domestic animals fall into two general classes, ruminants and nonruminants. The ox, sheep, goat, camel, llama, and buffalo belong to the former class; the other domestic animals belong to the latter. The stomach of nonruminants is relatively simple, consisting of only one compartment. For this reason it is frequently referred to as the simple stomach. That of ruminants is more complex, consisting typically of four compartments, only one of which secretes gastric juice. Digestion in the simple stomach will be described first, then in the ruminant stomach.

Among the simple-stomached animals are found carnivores, herbivores, and omnivores. The natural foods of these animals therefore vary greatly. Nevertheless, in stomach digestion in all animals there are many points in common. Since more is known about digestion in the dog than in any other animal, the dog will be used as the basis for the description of the processes in the simple stomach. The processes in the cat are very similiar to those in the dog. Certain features applying to the pig and the horse will be indicated in appropriate places.

Functions of the Stomach. The stomach is not only an organ in which important factors of digestion operate; it is also a reservoir for swallowed food. Furthermore the stomach produces an "intrinsic factor." probably an enzyme, which acts on an "extrinsic factor" in the food to produce the erythrocyte-maturing factor, or antianemic principle (p. 31). The stomach therefore functions in hematopoiesis.

Observations on the effect of complete removal of the stomach (gastrectomy) indicate, however, that the organ is not essential to life. Gastrectomy has been performed on animals of several species (rat, dog, pig, monkey) and the results indicate clearly that, with the possible exception of the rat, the stomach is a dispensable organ. Ivy (1940), who has studied and reviewed the effects of gastrectomy in animals, points out, however, that removal of the stomach imposes a number of burdens on the organism; among them, (1) a reduction of the factor of safety in digestion, (2) a strain on the digestive and absorptive functions of the intestine, (3) pressure on the calcium stores of the body, which results from the acid tide that develops during digestion in the gastrectomized animal, (4) a tendency to develop anemia (not pernicious anemia).

The effects of gastrectomy are more severe in growing and pregnant animals. Any gastrectomized animal must receive adequate nutritional care.

REGIONS OF THE GASTRIC MUCOUS MEMBRANE

The stomach is a hollow, saclike organ whose wall is made up of four coats. From without inward these are the serous and muscular coats, the submucosa, and the mucous membrane. The mucous membrane is clearly divisible into several zones, most of which contain glands. Usually three gland zones—cardiac, fundic, and pyloric—are present, and in some animals a glandless esophageal region is found.

In the horse the esophageal region is large, making up one-third to two-fifths of the mucous surface. It is nonglandular and is covered with stratified squamous epithelial cells continuous with those of the esophagus. The cardiac gland zone is below the esophageal part and is very narrow. The fundic gland zone is large. The pyloric gland zone extends to the pylorus. It corresponds to the pyloric part of the stomach of the dog and of man.

In the pig the esophageal region is limited to a small area around the cardia. The cardiac gland zone is very extensive, occupying the left extremity of the stomach. The fundic and pyloric gland zones are comparable in position to those of the horse.

In the dog the esophageal region is lacking. The cardiac glands are found in a narrow zone around the cardia and are also scattered along the lesser curvature. The fundic gland zone is extensive, occupying about two-thirds of the gastric mucous membrane including that of the left extremity or fundus. The pyloric gland zone occupies the remainder of the mucous membrane.

GASTRIC GLANDS

The gastric glands are located in the mucous membrane and open upon its surface by numerous orifices. They are tubular or branched tubular in type. Three main classes of gastric glands are distinguished: cardiac, fundic, and pyloric.

Cardiac Glands. These occupy the cardiac gland zone. Considerable controversy has existed regarding the significance of the cardiac glands, especially in the pig. Bensley expressed the opinion that they are mucus-secreting glands and therefore do not produce enzyme. According to this worker they are to be regarded as retrogressive structures derived from the fundic glands and destined ultimately to disappear. If this is true, it may afford an explanation of the absence of glands in the extensive esophageal region of the horse. This may simply be a zone from which glands have disappeared in the course of evolution. Ellenberger and Scheunert reported that, contrary to their earlier views, the cardiac glands of the pig do not secrete an amylase. This was determined from studies on the secretion obtained from an experimentally produced fistulous pouch of the cardiac gland zone.

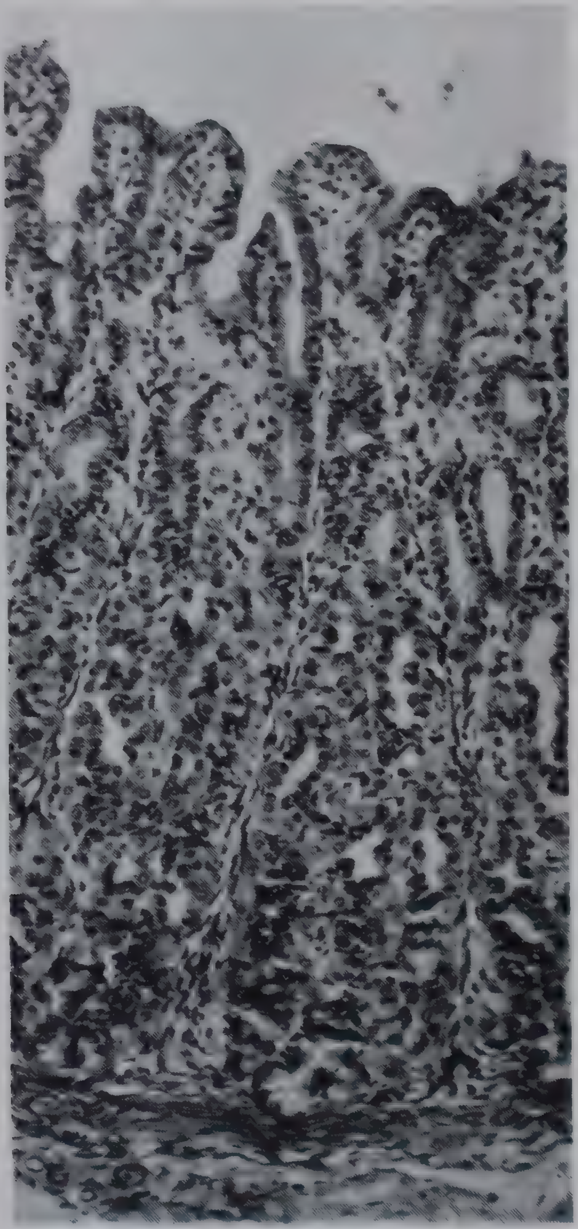


FIG. 74.—Photograph of fundic glands of pig. The parietal cells appear lighter than the chief cells. (Courtesy of Dr. Margaret Sloss.)

Fundic Glands. These are the proper gastric glands (Fig. 74). The gland cells are of three main kinds: body chief cells, neck chief cells, and parietal cells. The body chief cells are undoubtedly the enzyme producers. Their so-called zymogen granules are generally assumed to be the substance from which enzyme is derived, although definite proof is lacking. The neck chief cells line the upper part of the gastric glands. They are believed to be mucus-secreting cells. According to Bensley, they are essentially similar to the cells of the cardiac and pyloric glands. The parietal or border cells are generally regarded as being the producers of the hydrochloric acid of the gastric juice.

Pyloric Glands. These are found in the pyloric regions of all stomachs. Parietal cells are lacking. The secretion of these glands contains mucus and a small amount of a proteolytic enzyme. Lim and Dott studied the secretion by isolating the pyloric segment of the stomach of the dog and forming the segment into a pouch opening to the outside. The secretion was found to be viscid, scanty, and slightly alkaline. It contained a proteolytic enzyme only a twenty-fifth as active as pepsin secreted by the fundic glands. These workers state that the proteolytic action of an extract of the pyloric mucous membrane of the calf has been found to be only one-twentieth of that of fundic extract; of the pig only one-fortieth.

GASTRIC JUICE

By the term gastric juice is meant, strictly speaking, the secretion of the fundic glands. However, the term is sometimes extended to include also the secretion of the pyloric and cardiac glands. The secretion of the fundic glands is so important physiologically that it may be considered in detail.

Methods of Obtaining Gastric Juice. Pure gastric juice cannot be obtained merely by use of the stomach tube nor by means of a simple fistula of the stomach. In such cases the juice is likely to be mixed with saliva, mucus, pyloric secretion, food, and regurgitated intestinal juices. Hence the pure secretion must be obtained in some other way.

Several extensive studies have been made on men with gastric fistulas. Beaumont's study of Alexis St. Martin is a classic in physiology. St. Martin had a gastric fistula that resulted from a gunshot wound. Accidental occlusion of the esophagus as a result of the ingestion of some caustic substance may necessitate the making of a fistulous opening into the stomach, through which the patient feeds himself by inserting previously masticated food. Studies of several such cases are on record. Carlson and associates (Carlson, 1916) studied such a case over a period of years at the University of Chicago. As a result of the sensations of eating, gastric juice is secreted, and this may be obtained through the fistulous opening. In animals gastric juice may be obtained by the following experimental procedure: A fistula is made into the stomach; then the esophagus is fistulized in such a way that the upper and lower parts communicate with the outside through openings in the neck (Fig. 75). When the animal is fed, the meal does not enter the stomach but falls out of the upper opening in the neck. Yet, as a result of the stimulus of eating, gastric juice is secreted and it passes out through the stomach fistula. Barring admixture with intestinal contents, juice so obtained is pure, although of course it is not composed solely of fundic secretion. This operation was devised by Pavlov, who performed it on dogs.

Better than the esophageal–gastric-fistula method for many purposes is another procedure of Pavlov in which a part of the fundus of the stomach is made into a pouch opening to the outside through the abdominal wall (Fig. 76). The pouch is left attached to the main stomach, but their cavities are entirely separate. The pouch has an adequate blood supply and the sympathetic innervation is not disturbed. The general belief has been that the vagal innervation of the pouch is largely intact. Recent work indicates, however, that when the Pavlov pouch is made in the usual way the bulk of the vagus nerve supply is abolished (Jemerin and Hollander). Technics have been devised for making stomach pouches possessing an unquestioned vagal innervation (Hollander and Jemerin; Neuwelt, Olson, and Necheles; Thomas).

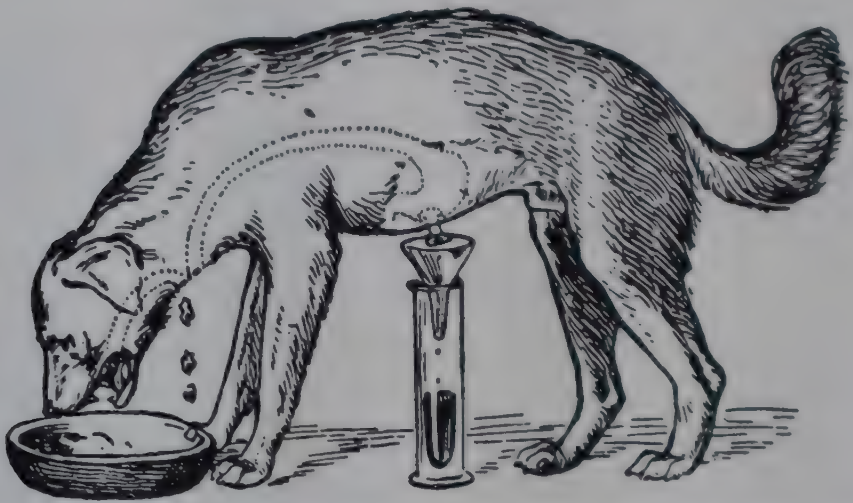


FIG. 75.—Fistulas of esophagus and stomach. When the dog eats, food does not enter the stomach but falls out of the lower end of the upper part of the esophagus. However, gastric juice is secreted, under the influence of cephalic stimuli, and can be collected as it flows out of the cannula in the stomach. The dog is fed through the opening into the lower part of the esophagus or through the stomach fistula. (Höber; from Winton and Bayliss' *Human Physiology*.)

The Heidenhain pouch (Fig. 77) is similiar to the Pavlov pouch except that it is completely separated from the main stomach. Its vagal nerve supply is thereby abolished. Many other kinds of stomach pouches have been devised. Gastric pouches have been made in animals of a number of species including ruminants.

The gastric pouch secretes gastric juice in unison with the main stomach. From the pouch, or miniature stomach, the pure juice may be obtained.

Composition and Action. Pure gastric juice is a clear, colorless, watery secretion of a distinctly acid reaction and taste. Its specific gravity in the dog is 1.002 to 1.004 or more, in the goat 1.006, in the calf 1.002 to 1.003. It consists of water, organic substances, inorganic salts, and hydrochloric acid. The accompanying table (Rosemann) shows the details of its composition in a dog. The juice was obtained by sham-feeding a dog having a divided esophagus and a gastric fistula.

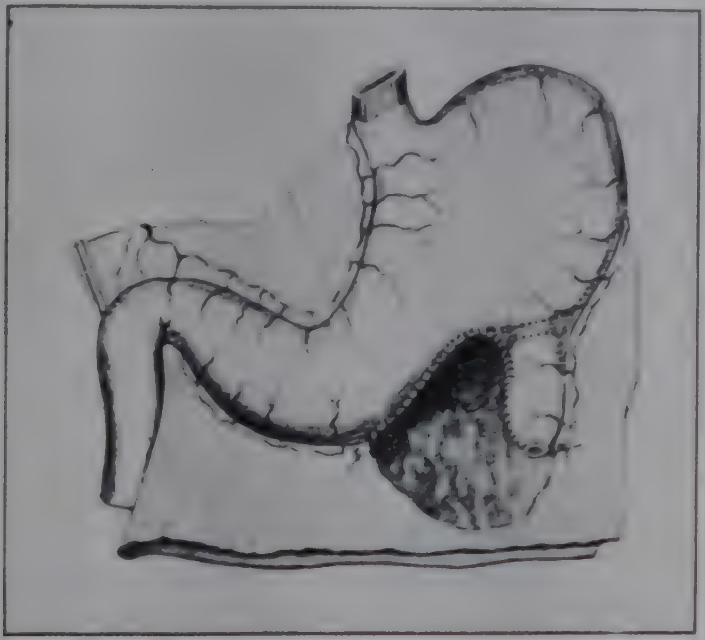


FIG. 76.—Diagram of the Pavlov or fundic pouch. The pouch communicates with the outside through an opening in the wall of the abdomen. The dotted lines at the base of the pouch indicate the double septum of mucous membrane constructed there. (From Lim and Dott, *Quarterly Journal of Experimental Physiology*, 1923, 13.)

Specific gravity	1.002 to 1.004
Freezing point	—0.638 to —0.490° C.
Dried residue	0.4277 per cent
Ash	0.1325 per cent
Organic matter	0.2944 per cent
Total Cl	0.6137 per cent
Titratable HCl	0.5472 per cent
Cl in ash	0.0653 per cent
K, Na, Ca, Mg, Fe	small amounts

The *p*H of pure gastric juice obtained from a stomach pouch of the dog is slightly less than 1.

As a part of the organic matter of gastric juice at least three enzymes are found: pepsin, rennin, and gastric lipase.

Pepsin. This is a proteolytic enzyme formed in the body chief cells of the fundic glands. It is found in the stomach of all vertebrates. It exhibits the general properties of enzymes, and may be extracted with water or other solvents from the fundic mucous membrane. It has been prepared in crystalline form. Crystalline pepsin is a protein. Before pepsin can produce its action of hydrolyzing protein it must be activated. This is accomplished, in the stomach, by hydrochloric acid. Contrary to the former view, the activation by hydrochloric acid is now believed to be nonspecific and due simply to the establishing of a favorable hydrogen ion concentration for the action of pepsin (Waldschmidt-Leitz). The optimum *p*H for the action of pepsin varies somewhat with different proteins and ranges from approximately *p*H 1.5 to 3. Pepsin in this favorable acid medium converts proteins into simpler products as follows:

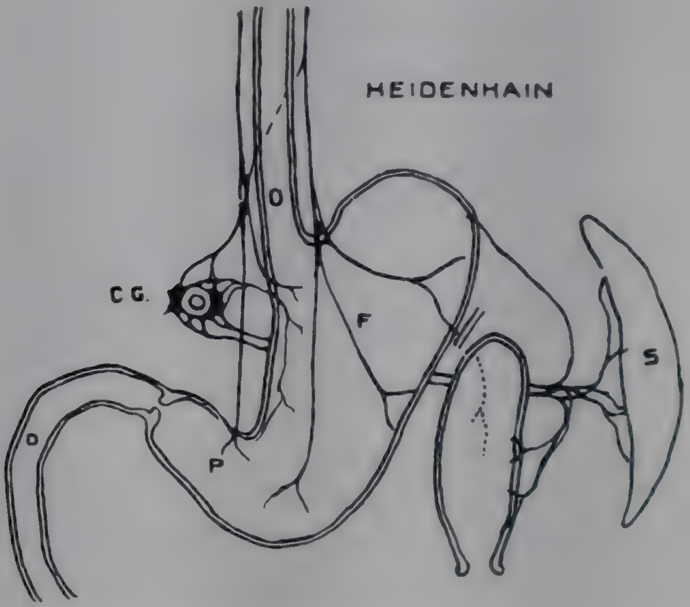


FIG. 77—The Heidenhain pouch. Note that it is completely separated from the main stomach. The dotted line indicates degenerated vagal nerve fibers. The sympathetic fibers are intact. (From Lim, Ivy, and McCarthy, *Quarterly Journal of Experimental Physiology,* 1925, **15.**)

$$\begin{tikzcd}[row sep=small] \text{Native protein} \arrow[d] \\ \text{Acid metaprotein} \arrow[d] \\ \text{Primary proteoses} \arrow[d] \\ \text{Secondary proteoses} \arrow[d] \\ \text{Peptone} \end{tikzcd}$$

Proteoses and peptone require complete, or nearly complete, hydrolysis to amino acids before absorption, but such hydrolysis is not accomplished in the stomach. It is said that amino acids result from peptic–hydrochloric-acid action only when the action is continued for a much longer time than is available during the sojourn of the food in the stomach. The complete hydrolysis of the peptic–hydrochloric-acid digestion products is accomplished by enzymes in the intestine.

Rennin. This is a milk-coagulating enzyme found in the gastric juice of the calf and possibly other young ruminants. For years it was thought that a similar enzyme was found in the gastric juice of all young mammals. Present evidence does not support the latter view. The milk-coagulating enzyme of the gastric juice of other mammals is apparently the same as pepsin. All proteinases have the power of clotting milk, but they carry the action on casein much beyond that caused by rennin. The action of rennin is to change casein to paracasein. Calcium ions then react with paracasein to form the gel calcium paracaseinate. The steps may be represented as follows:

Casein + rennin = paracasein (soluble)
Paracasein + Ca = calcium paracaseinate (coagulum)

The advantage in digestion of having milk coagulated in the stomach is probably to delay its passage through the stomach. In this way the action of pepsin on the milk proteins would be prolonged. Rennin is activated by hydrochloric acid. It has been prepared in crystalline form.

Gastric Lipase. This enzyme, reported in 1900, occurs in small amounts in pure gastric juice. Its concentration in the juice of the dog is five or six times that of lipase in the blood (Hull and Keaton). Its presence in gastric juice is therefore not incidental to the presence of lipase in blood. Gastric lipase is most abundant in carnivores and rodents, almost absent in fish and birds, and practically absent in ruminants (Haurowitz and Petron). Its action is to hydrolyze fats into their constituent fatty acids and glycerol, but it is doubtful if this action extends beyond fats ingested in a state of emulsification, for example, milk fat; for the amount of lipase is too small for the enzyme to make much impression on unemulsified fats. Fat digestion is accomplished mainly by pancreatic lipase in the intestine. The optimal *p*H for the action of gastric lipase of several domestic animals is as follows (Haurowitz and Petron): dog, 6.3; cat, 5.5; rabbit, 6.3; pig, 7.1; sheep, 6.3; horse, 7.5.

Hydrochloric Acid. This important constituent of gastric juice appears, like pepsin, to be present in all vertebrates. It is produced by the parietal cells of the fundic glands, but the manner in which these cells give rise to a strong acid, hydrochloric, is uncertain. According to one point of view the cells are the direct producers of the acid. According to another, though the cells may produce the forerunners of acid, they do not produce the acid itself, the cells being in fact slightly alkaline in reaction; the acid is not produced until the precursor reaches the crypts of the glands. Work by Dawson and Ivy, in which they removed pieces of mucous membrane from an actively secreting gastric pouch and quickly examined them microscopically, reveals that there is a primary stage following removal of the pieces during which the parietal cells are acid to neutral red. In some cases the neutral red was given intravenously and in others the pieces of mucous membrane were immersed in the stain prior to examination. These experiments lend support to the view that the parietal cells are the direct producers of the acid.

The chemical or physicochemical changes involved in the production of hydrochloric acid by the parietal cells are not known. A number of hypotheses have been proposed, but a generally acceptable theory is lacking. For details textbooks of biochemistry may be consulted. See also the review by Gray.

Carbonic anhydrase (p. 225) is present in the parietal cells of the gastric glands but there is no clear evidence that it is an essential part of the mechanisms having to do with the production of hydrochloric acid (Davenport).

The concentration of hydrochloric acid in the pure gastric juice of the dog is about 0.55 per cent (Rosemann). Its concentration in the stomach contents varies with the nature of the food, the stage of digestion, the amount of saliva to be neutralized, and other factors. When protein predominates, hydrochloric acid accumulates more slowly because the first acid secreted combines with protein. As digestion proceeds the concentration of hydrochloric acid in the stomach is kept down by the regurgitation of alkaline fluids from the duodenum (Boldyreff).

While hydrochloric acid is the only acid produced by the gastric glands, it is not the only one found in the stomach. In herbivores, where the concentration of hydrochloric acid in the gastric juice appears to be less than in omnivores and carnivores, considerable amounts of organic acids (acetic, butyric, lactic, and others) may be present because of bacterial action on food carbohydrates. The contents of the stomach of the horse have been shown to vary in reaction from *p*H 1.13 to 6.8 (Schwarz, Steinmetzer, and Caithaml).

The functions of hydrochloric acid may be summarized as follows: (1) It activates pepsin and rennin. (2) It co-operates with pepsin in the digestion of protein. (3) It may bring about a slight hydrolysis of sucrose; however, this function is unimportant. (4) It acts as a stomach antiseptic, although the importance of this action is probably overestimated (Carlson, 1923).

CONTROL OF GASTRIC SECRETION

In man and apparently in the horse (p. 294) the secretion of gastric juice is a continuous process. In the dog it is intermittent. The cause of the continuous secretion is unknown. The rate of secretion increases when food is eaten.

The question as to how the gastric glands are excited to the marked activity that accompanies and follows a meal has received much attention. It has been recognized for years that at least two kinds of stimuli—nervous and chemical—are involved. Recent work (Lim, Ivy, and McCarthy; Ivy, 1930, 1942) has added greatly to our knowledge of the control of gastric secretion and has served to clear up much of the confusion of the past. The secretion may be divided into three phases—cephalic, gastric, and intestinal—depending upon the place of origin of the stimuli.

Cephalic Phase. As a result of the sensations of eating, nerve impulses are discharged from a gastric secretory center to the gastric glands. Secretory fibers to the glands are contained in the vagi, for transection of these nerves abolishes the cephalic phase. This phase takes place even when no food is permitted to enter the stomach, as when an animal with a divided esophagus is fed a sham meal. The latent period for the secretion is, in the dog, usually four or five minutes. The stimuli arise largely because of a psychic state developed as a result of the sensations of eating, but in view of the fact that a decerebrate dog will secrete gastric juice when fed a sham meal, the term psychic is not entirely applicable. It is therefore better to use the word cephalic. This phase of gastric secretion appears to be absent in herbivores.

Gastric Phase. When food enters the stomach a much more copious secretion takes place. This secretion can be demonstrated by feeding a dog provided with a Pavlov or some similiar pouch, whereupon a free flow from the pouch results. In the dog, following a meal of meat, the maximum secretion is attained in one hour, after which it diminishes, at first sharply and then more gradually, to the fifth hour (Pavlov). The gastric phase of gastric secretion is due to at least two kinds of stimuli, mechanical and humoral.

Mechanical Stimulation. When food or even inert substances come in contact with the stomach mucous membrane, a flow of gastric juice is set up. This flow might be caused by stimulation of the gastric glands through a local nervous mechanism or by an increase in the blood supply to the glands, although definite knowledge is lacking.

Humoral Stimulation. That the gastric glands are excited by chemical substances present in the food or produced during gastric digestion was made probable by the work of Pavlov, Edkins, and others. Edkins showed that extracts made by treating pyloric mucous membrane with weak hydrochloric acid, boiling water, peptone, or glucose would, when injected into the blood stream of an animal, cause a flow of gastric juice. He believed that the products of digestion acting on the pyloric mucous membrane caused the development of a substance (gastrin) which when absorbed into the blood stimulated the fundic glands to activity. While the correctness of Edkins' observations have not been questioned, his methods and conclusions have been criticized in recent years. But that his views of a chemical excitant for the gastric glands acting through the blood stream (humoral mechanism) were correct in principle is indicated by the work of Ivy and Farrell (1925) in which a small stomach pouch was permanently transplanted under the mammary gland. When the dog was fed, the pouch secreted gastric juice. Clearly, when food was consumed something (from the stomach, the intestine, or both) entered the blood stream and was conveyed to the transplanted pouch, causing it to secrete. Lim and Necheles have supplied evidence that a humoral mechanism is concerned in gastric secretion. They passed through a dialyzer the circulating blood of dogs during digestion. When the dialyzate was injected into other dogs, gastric juice was secreted. Experiments such as these leave no doubt that a chemical stimulus carried by the blood stream is concerned in gastric secretion. But the question whether the stimulus is a hormone has not been decisively answered. Indirect evidence (Gregory and Ivy) has been obtained that the gastric component of the humoral mechanism is a hormone. Experiments by Sacks and co-workers suggest that histamine is the gastric hormone, or one component of it. Histamine occurs in the gastric mucosa in considerable amounts. Injected into an animal, histamine is a very powerful stimulant to gastric secretion. Evidence against the view that histamine is the gastric secretory hormone has been obtained by several workers (Komarov, MacIntosh).

Intestinal Phase. That an intestinal phase of gastric secretion is present has been shown in the following way: A pouch of the entire stomach of a dog was made and the esophagus was joined to the duodenum. When the dog was fed, food entered the intestine directly, and a copious flow of gastric juice took place within an hour. Evidently something in the food, or, more likely, something formed during digestion of the food, entered the blood stream from the intestine and stimulated the gastric glands to activity. Other evidence has been obtained that the humoral excitant for the gastric glands includes a component liberated from the intestinal mucosa (Gregory and Ivy).

Secretion and Function of Mucus. Gastric mucus is derived from the cardiac and pyloric glands and the neck chief cells of the fundic glands. According to Carlson (1923), the secretion of gastric mucus is a process largely independent of the secretion of water, hydrochloric acid, and enzymes. Stimulation experiments (Jennings and Florey) reveal that the vagus nerve controls the secretion of mucus by these structures. The surface epithelial cells of the stomach apparently do not respond to vagal stimulation. Mucus functions by physically protecting and lubricating mucous membranes, and possibly in other ways (Ivy).

Inhibition of Gastric Secretion and Motility: Enterogastrone. When fat or sugars are ingested in sufficient amounts, gastric secretion and motility are inhibited. This inhibition has been shown by several groups of workers to be caused by a hormone, *enterogastrone,* formed in the intestine and carried to the stomach by the blood. Gray, Bradley, and Ivy have described a method for the preparation of an extract of duodenal mucosa of the pig which shows an inhibitory effect on both gastric secretion and motility. In later studies Gray and co-workers obtained evidence suggesting that enterogastrone is two principles, one inhibiting secretion, the other inhibiting motility.

Normal urine has been shown to contain a substance which exerts an inhibitory action on gastric secretion. It has been designated as *urogastrone*. It is apparently not identical with enterogastrone.

OTHER BIOCHEMICAL PROCESSES IN THE STOMACH

Certain digestive changes are brought about in the stomach by agents that are not a part of gastric juice. In the stomach of man salivary digestion of starch is continued for 15 to 30 minutes or more; it is stopped by hydrochloric acid. Somewhat similar conditions probably prevail in the stomach of the pig, though the amylolytic action of pig's saliva is much weaker than that of human saliva.

In the stomach of herbivores, bacteria (Scheunert and Schieblich) and plant enzymes (Scheunert, 1925) begin their work. As hydrochloric acid accumulates, their action is inhibited. Bacteria attack mainly cellulose, but other carbohydrates and proteins do not escape their action. Bacterial digestion of cellulose is discussed elsewhere (p. 326). The action and significance of plant enzymes in digestion have not been extensively studied. They may be of some importance in the stomach of the horse and pig.

THE FILLING OF THE STOMACH

The stomach possesses a remarkable power of adapting its size to the amount of ingesta in it (Grey). The empty stomach is contracted and tubular in form and is bent upon itself at the junction between the fundus and pyloric portions—the incisura angularis. That such is the case in carnivores and man is indicated by roentgen-ray studies. It is only when the stomach is more-or-less filled with food that it assumes its well-known comma or piriform shape. Even in this condition the intragastric pressure is not normally high, the stomach musculature having relaxed in order to accommodate the food. The stomach of the horse and of other herbivores does not empty itself between meals but only after a fast of considerable duration. What shape the empty stomach of the horse assumes is not known, but it is not likely that its postmortem shape when empty represents the condition in life.

Studies by Ellenberger, Scheunert, and others (reviewed by Sisson, 1914b, 1923b) show that in the stomach of the horse there is a marked tendency for the food to arrange itself in strata in the left extremity and body. It is only in the pyloric part that mixing or churning takes place. Cannon (1911) has shown that a similar condition is present in the stomach of the cat. Work by Scheunert and Kiok shows that as regards stratification the stomach of the pig behaves similarly to that of the horse; the strata remain for many hours. Even in the stomach of man there is some tendency toward stratification.

In the horse the first food consumed passes into the ventral region of the stomach. Subsequent arrivals of food lie on previous arrivals in the form of layers or of piles, or they settle into or around them, depending on the physical character of the food. These facts were shown by feeding horses with a series of artificially colored foods and later killing the horses, removing and freezing the stomachs, and studying the arrangement of the contents. In order to mark the food remaining in the stomach from the previous meal, the horses were given water colored with malachite green in the morning before feeding. In this way it was found that the food remaining from the last meal occupied about a third of the stomach and lay along the greater curvature and in the pyloric and fundic regions. The amount varied in different subjects and with different diets, and was in some cases a little more than 7 kg.

In view of the stratification of ingesta in the stomach of the horse and the fact that the stomach is not large enough to hold an ordinary meal and any considerable quantity of water, a question has arisen concerning the effect on gastric digestion of watering horses when the stomach is full. Scheunert studied this question by feeding horses and later giving them water so colored that its distribution in the stomach and intestines could be seen upon postmortem examination. Among the conclusions reached by this investigator are the following: (1) The drinking of water in any amount desired by the animal causes no harmful effect on digestion. (2) The increase in the water content of the stomach ingesta is not over 10 per cent above the ordinary water content. (3) Most of the water passes out of the stomach quickly. (4) When the stomach is well filled the water enters the contents very superficially. Little or no water finds its way into the left extremity. It apparently passes first to the central part of the stomach and thence along each side and the greater curvature to the pylorus. (5) Only when the stomach contains little food is the mass penetrated throughout by the water drunk. Further experiments showed that no washing out of food from the stomach occurred when horses which had been fed were watered. Evidently, then, the arrangement of food in the stomach of the horse is not seriously disturbed by water drinking. Similar conclusions have been reached by Linton and by Bergman. It is said that in the dog and man likewise water drinking has little effect on the arrangement of the gastric contents.

Trautmann and Schmitt studied the amount of the stomach contents of pigs by means of cannulas inserted into the stomach. The animals did well during the studies which extended over several weeks. The amount of the stomach contents was subject to variation in the same pig on different days in spite of identical treatment and feeding. Variations among individuals were also noted.

THE EMPTYING OF THE STOMACH

The stomach of carnivores may practically empty itself between meals, whereas that of herbivores requires a fast or many hours' duration before it is empty. In the horse, according to Ellenberger and Hofmeister, at least 24 hours are required. Roentgen-ray observations indicate that the stomach of the pig still contains food after a day's fast (Neimeier).

It is now a well-established fact that the food does not remain imprisoned in the stomach for several hours to be suddenly discharged into the intestine. The emptying of the viscus is a progressive process during the entire course of stomach digestion (Fig. 78). At frequent, irregular intervals ingesta from the stomach are forced into the intestine by contractions of the stomach that raise the intragastric pressure above that in the duodenum. The pyloric sphincter was formerly thought to be of great importance in determining the passage of ingesta from the stomach into the intestine. At present less significance is attached to this mechanism. That the pyloric sphincter is not of great importance in gastric emptying is indicated by the fact that its surgical removal does little or no harm. Likewise the waves of peristalsis in the stomach probably do not have much to to with the pushing of ingesta into the intestine until they reach the distal half of the pyloric antrum. Before they reach this point the advancing waves do not elevate the pressure in the region of the sphincter and therefore do not cause propulsion of material from stomach to intestine. Normal evacuation of material from the stomach requires an adequate pressure gradient from stomach to duodenum. Otherwise the resistance to evacuation will not be overcome and material will not pass out. When the peristaltic wave reaches the middle of the antrum, sufficient pressure is produced to force material through the open pylorus under low pressure into the duodenum. Peristaltic waves that fail to create enough pressure to force material into the duodenum may neverthless cause mixing of the gastric contents. This would apply to waves traveling from their origin in the region of the incisura angularis to the middle of the antrum. If the wave progresses beyond the middle of the antrum it is likely to create enough pressure to overcome the resistance to evacuation. As a wave approaches the pylorus—that is, after the wave has passed the middle of the antrum—the sphincter begins to contract and the resistance to evacuation is increased. But the pressure in the antrum now rises sharply and effective evacuation therefore continues. The sphincter closes and the

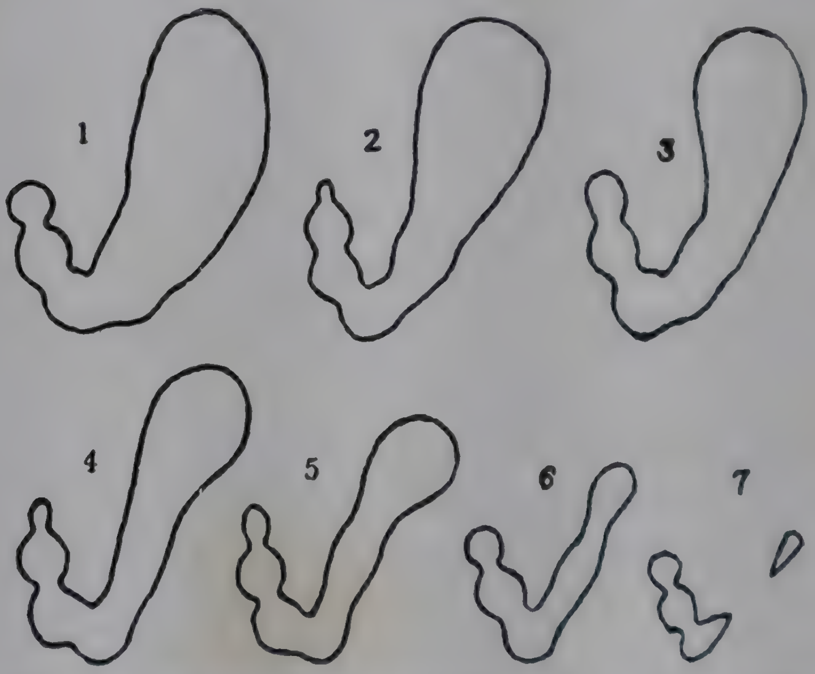


FIG. 78.—Changes in the shape of the stomach of a cat at intervals of an hour during the digestion of a meal, as revealed by tracings of the shadow cast on the fluorescent screen. (From Alvarez' *The Mechanics of the Digestive Tract*, Ed. 2. Paul B. Hoeber, Inc.)

duodenal bulb contracts and forces ingesta down the duodenum. Closure of the sphincter is not essential to ending the evacuation cycle, for by the time the sphincter closes the antrum is already empty.

Much of this description is based on recent work on dogs by Quigley, who has successfully used modern methods of pressure recording in studies of intraluminal pressures in gastric emptying and gastro-intestinal propulsion. Quigley asserts that gastric emptying is determined mainly by the work of the antral pump—an effective pressure gradient from antrum to bulb. Antral tone, the frequency and size of antral peristaltic waves, and whether the waves die out or maintain themselves as they approach the sphincter—these are the main factors in determining the evacuation pressure. Antrum, sphincter, and bulb tend to work as a unit so far as motor activity is concerned. The pyloric sphincter is probably of more significance in preventing duodenal regurgitation than in regulating stomach evacuation. This does not mean, however, that regurgitation from the duodenum into the stomach never occurs. It certainly can occur under normal conditions.

The nerves of the pyloric sphincter are the vagus and sympathetic. Although it is probable that both nerves contain motor and inhibitory fibers for the sphincter, the vagus is mainly inhibitory and the sympathetic mainly motor (Nakanishi). The results obtained when the nerves of the sphincter are stimulated depend to a considerable extent upon whether the sphincter is relaxed or contracted at the time of stimulation.

Further information on the physiology of the pylorus will be found in Alvarez' book (1940).

THE SIGNIFICANCE OF GASTRIC JUICE IN THE HORSE

It has been estimated that a horse may swallow during a given meal two or three times the amount of material (food and saliva) remaining in the stomach at the close of the meal. The excess, together with the food remaining from the previous meal, must pass on into the intestine during the meal, the first food consumed being in general the first to pass out. This consideration means that a good deal of the food cannot remain long in the stomach and raises the question of the importance of stomach digestion in the horse. If Bensley's view is correct that the esophageal zone is one from which gastric glands have disappeared and that the cardiac glands are partially degenerated fundic glands, then one is inclined to hypothesize that the stomach of the horse is an organ in which gastric juice plays a part of limited importance. Such a view gains additional support from the fact that bacteria play an important role in the digestive processes in herbivores and that in solipeds the complex large intestine supplements the relatively simple stomach. But the hypothesis is somewhat weakened by the observation that the stomach of the horse secretes a very considerable amount of gastric juice (10 to 30 liters daily).

The horse is prone to digestive disorders of gastric origin. Possibly these are due in part to the transition through which the stomach seems to be going.

Gastric Fistula in the Horse. It is an old belief that it is practically impossible to establish a gastric fistula in the horse because of the peculiar location of the stomach with respect to the abdominal wall and the supposedly great susceptibility of this animal to peritonitis. The Russian investigators Egorov and Cheredcov have successfully challenged this view by establishing a gastric fistula in a horse. The fistula was of the simple type. The juice obtained from the stomach was therefore mixed with saliva and at times with regurgitated intestinal contents. Nevertheless these complications did not seriously affect the validity of the observations that were made.

The fistula was made in the fundic region of the stomach. At first a stomach cannula was used but later the stomach was sewed to the abdominal wall.

Under normal conditions of feeding the stomach was never empty. It always contained a mass of well-chewed food. After a day of fasting the stomach still contained particles of food; after a day and a half, it occasionally contained food particles; after 2 to 2½ days, it was completely empty.

The secretion of gastric juice was continuous even during a fast of two days. The juice was removed from the stomach by means of a rubber tube inserted through the fistula. The *empty* stomach secreted 10 to 30 liters of juice a day. The rate as determined during 10- or 15-minute intervals was not always constant. In one experiment in which the juice was removed from the stomach at 10-minute intervals, the following amounts were secreted in consecutive periods: 140 cc., 90, 130, 130, 100, 100, 100, 100, 130, 130, 130, 130, 125, 80, 110, 80, 115, 80, 120, 110, 110, 125, 130, 130, 90.

The sight of oats, the favorite food of the horse, did not cause any increase in the flow of gastric juice. Psychic secretion was therefore lacking. In fact, there was some evidence of a decrease in the secretory rate.

Mechanical stimulation of the stomach by means of a rubber tube passed through the fistula gave conflicting results on the rate of secretion. In later observations on this horse, however, mechanical stimulation was found to be effective in increasing the secretion of gastric juice (Poltyreff and co-workers).

Atropine caused regurgitation of intestinal contents into the stomach and a considerable decrease in gastric secretion.

Albumin in Mett's tubes was readily digested by the juice. The hydrochloric acid content of the juice was 0.14 to 0.21 per cent.

That the horse secretes gastric juice continuously during fasting has been confirmed by Troitskiĭ. This investigator observed continuous, though undulating, secretion in young horses (1½ to 2 years old) during fasts lasting several days. The observations were made by means of gastric fistulas and a Heidenhain pouch. The irregularities of secretion rate could not be related to external factors or conditioned reflexes.

GASTRIC JUICE OF THE PIG

Observations on the gastric juice of the pig have been reported by Gilde and by Heyenga, using fistulas of the stomach and of the esophagus.

Amylase was not found in the secretion obtained from the stomach. Pepsin was always present in the gastric juice. The amount was subject to considerable variation. Lipase was not always present. The acidity of the juice varied greatly. In two pigs the amount of juice secreted varied from 25 cc. to 300 cc. per hour. The dry matter of the juice varied from 0.9 to 2.4 gm. per cent; the ash content, from 0.4 to 0.8 gm. per cent.

Little or no secretion took place when the reflux of duodenal juice (into the stomach?) was prevented by ligation of the duodenum between the pylorus and the ductus choledochus. The conclusion was drawn that the reflux of duodenal contents (bile) is essential for the normal secretion of gastric juice in the pig.

Gastric secretion and digestion in unweaned pigs have been studied by Kvasnitskiĭ and Bakeevna, who made gastric fistulas in the pigs during their first day of life. Observations were continued over a period of two months.

STOMACH MOVEMENTS

During gastric digestion the stomach wall becomes the seat of important muscular movements whose action is to comminute the food, to mix it with gastric juice, and, at intervals, to pass it into the duodenum. Stomach movements have been extensively studied in the cat, dog, rabbit, and in man, but only to a limited extent in the pig and horse.

Methods of Studying Stomach Movements. Some of the methods by which stomach movements have been studied are as follows: (1) An important method is to immerse the opened abdomen of the animal in a bath containing warm physiological salt solution. The movements can be viewed through the clear solution. By means of threads, writing levers may be attached to different places on the stomach. The levers are then made to write on a kymograph. Also motion pictures may be made of the stomach's activity. The saline-bath method of studying stomach motility permits detailed observations to be made. (2) A balloon attached to rubber tubing may be introduced into the stomach, either by way of the esophagus or through a fistula of the stomach. The tube is then connected to a (water) manometer or other recorder, which writes on a kymograph (Fig. 79). In careful work it is important that the location of the balloon be accurately known. (3) The roentgen ray affords an excellent method of studying stomach movements. Barium sulfate is fed to the animal to cause the stomach contents to produce the desired shadow. In this method of study the animal is entirely normal. (4) Stomach movements may be studied directly through a fistula. (5) An opening may be made in the abdomen and a glass or celluloid plate fixed in the opening. Through the transparent plate, stomach movements can be seen. (6) Small pieces may be removed from the wall of the stomach and suspended in warm, oxygenated Locke's solution. Tracings of their contractions can be made (Fig. 80). (7) If an animal is killed and the abdomen quickly opened, stomach movements may be seen for a time. Naturally the question arises whether the movements so observed represent the normal condition. (8) Quigley (1944) has successfully used modern optical methods of pressure recording in studies of stomach and intestinal motor activity.

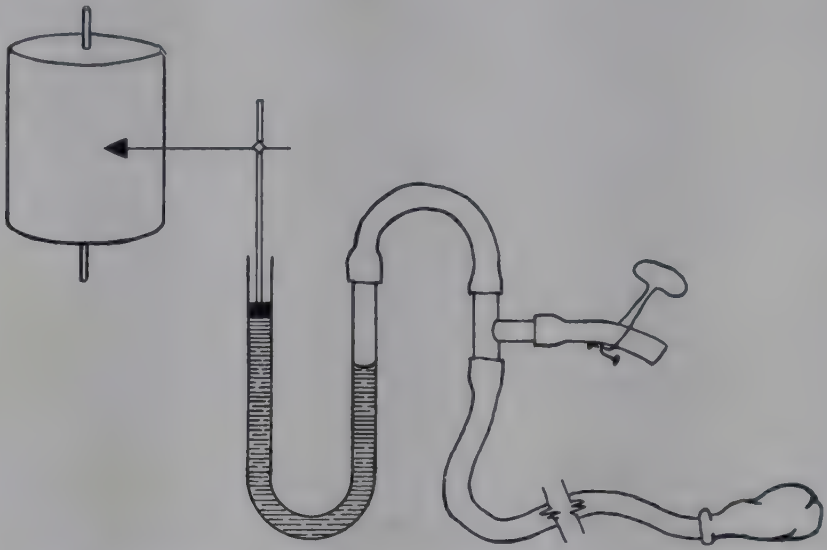


FIG. 79.—A simple method of recording stomach motility. The rubber tube is connected at one end to a small balloon and at the other end to a manometer (water, bromoform) arranged to write on a kymograph. The balloon is introduced into the stomach, either by way of the esophagus or through a gastric fistula.

All these methods of studying stomach movements may be applied also to the study of intestinal movements.

Kinds of Stomach Movements. Although an enormous amount of work has been done on stomach movements, there is as yet no complete agreement as to their exact nature. Cannon's roentgen-ray studies, extending over a number of years, added much to our knowledge of gastrointestinal movements. The more recent studies of Alvarez (1928, 1940), in which were made multiple tracings and motion pictures of stomach and intestinal movements, reveal that the problem is more complex than is usually taught. Studies by M'Crea, M'Swiney, Stopford, and Morison show that the same type of movement does not predominate in all animals. The careful work of Quigley on intragastric pressures and gastric evacuation has already been referred to. In spite of the complexity of the movements and our lack of knowledge as to their exact nature, many generalizations are well established.

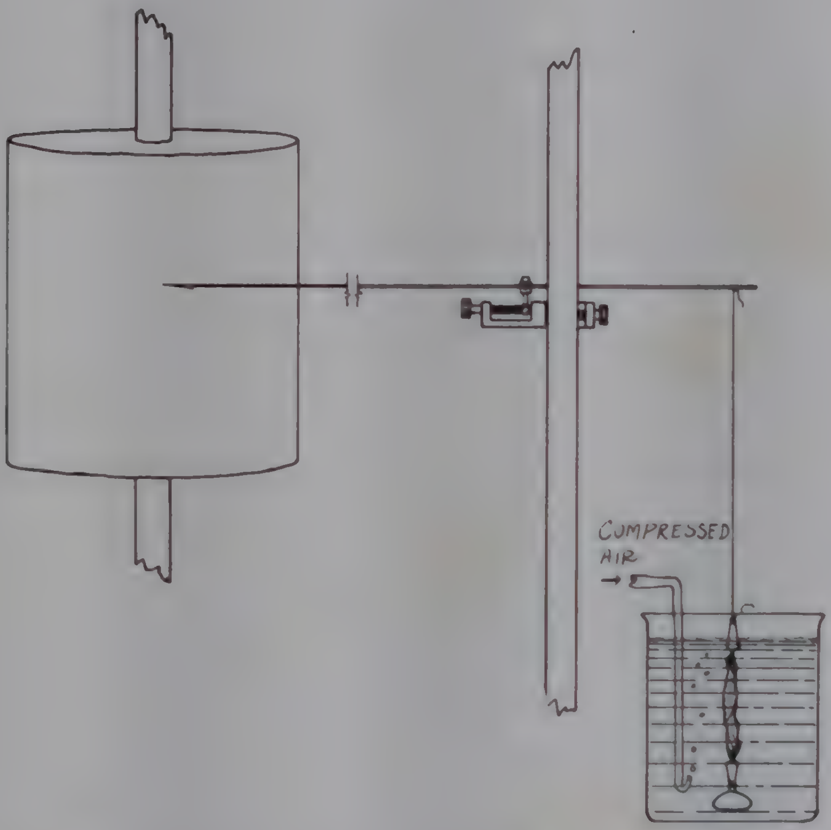


FIG. 80.—A method of recording motor activity of bits of stomach musculature or of segments of intestine.

The best-known stomach movement is a peristaltic wave beginning near the middle of the body of the organ and running toward the pylorus. Whether such waves pass right to the pylorus or stop a short distance before they reach it and give way to systoles and diastoles of the pyloric part, is a question. It is probable that the disagreement among workers is attributable in part to the failure of some to recognize that there are differences among the species. M'Crea, M'Swiney, Stopford and Morison point out that in the rabbit, dog, and man the type of movement characterized by peristalsis of the body and systole and diastole of the pyloric part is predominant. This type is less common in the cat; in this animal the common type is the one in which the peristaltic wave travels right to the pylorus. This latter type occurs also in man and the rabbit but not in the dog. Either type of movement would cause active churning of the food in the pyloric part. The relation of movements in the pyloric antrum to gastric evacuation has already been discussed (p. 291). The frequency of the peristaltic waves in the stomach of the rabbit, dog, and man is three or four per minute; of the cat, five or six per minute.

The fundus and the upper part of the body of the stomach do not show peristaltic waves, but the musculature of these regions may manifest tonic contraction.

By means of motion pictures Alvarez and Zimmermann (1928) have shown that other kinds of stomach contractions are present. They describe shallow, nearly stationary contractions, contractions of local origin superimposed on traveling ones, relaxation waves, occasionally waves of reverse peristalsis, etc. The signficance of all these types of activity has not been determined.

Schalk and Amadon (1921) made a series of gastric motility studies in the *horse* by the balloon-manometer method. The balloon and its attached rubber tubing were introduced into the stomach by the nasal passage, pharynx, and esophagus. They found it difficult or impossible to interpret the tracings owing to inability to determine the position of the balloon in the stomach. Attempts to locate the balloon (in small horses) by the use of the roentgen ray were unsuccessful. The usual motor response of the hungry stomach to food entering it was powerful contractions. In some animals, however, feeding was followed by quiescence lasting for hours.

Neimeier studied gastro-intestinal movements in young *swine* by means of the roentgen ray. Peristaltic waves began during feeding and increased in strength as they traveled toward the pylorus. Not all of the waves resulted in the expulsion of ingesta into the duodenum. About an hour after feeding the waves usually became less frequent, but there presently followed a period of increased stomach activity which usually lasted until three hours after feeding. The filled stomach showed a gas bubble in the upper part. The middle part contained fluid material, and the lower part the more compact shadow-casting medium.

Nervous Regulation of Stomach Movements. The stomach, so far as its muscular activity is concerned, possesses a high degree of automaticity. In this respect it is somewhat like the heart. That stomach movements are automatic may be shown by cutting all the nerves to the stomach or, better, by removing the viscus from the body and placing it in a suitable environment such as a moist chamber or a bath of Locke's solution. In either instance motor activity continues. As with the heart, so with the stomach, the question of myogenesis and neurogenesis of the movements presents itself. Are stomach movements the result of automatic stimuli arising within the nerve cells (myenteric plexus) of the stomach wall and then passing to the muscle cells, or do the muscle cells generate their own stimuli? A positive answer cannot be given at present, although the finding that the movements are not stopped by nicotine, which is believed to paralyze the myenteric plexus, strongly suggests that they are myogenic. In fact, a number of considerations make it probable that rhythmic muscular activity in general is myogenic (Alvarez, 1928). The neurons of the plexuses in the wall of the stomach probably have two functions: some of them are on the course of the vagus pathways to the stomach and others enable local reflexes to take place.

Notwithstanding the fact that the stomach movements are automatic, the stomach, like the heart, has an extrinsic nerve supply. The nerves are the vagi and splanchnics. The vagi are usually stated to be the motor nerves and the splanchnics the inhibitors, but recent work shows that the distinction between the two is not so sharply defined as was formerly thought. Experiments on stimulation of the extrinsic nerves of the stomach show that mixed effects can be obtained from either the vagus or the sympathetic supply. Probably the tonus conditions prevailing in the musculature at the time of stimulation are factors determining the different responses. The extrinsic nerves affect not only the motor activity of the stomach but also the tonus of the musculature. This is particularly true of the splanchnic nerves. There is little evidence of direct antagonism between the vagus and splanchnic nerves in their action on the stomach. Certainly such a definite antagonism as is seen in cardiac regulation is not evident here. In the stomach, as in other organs supplied by autonomic nerves, chemical mediators are believed to transmit the nerve effects to the responsive cells.

The normal function of the extrinsic nerves is therefore not to give origin to the stomach movements but to regulate them. They contain both afferent and efferent fibers, and it is through these and the central nervous system that correlation between the stomach and the rest of the organism is effected. Some of the efferent nerve fibers regulate stomach movements, as just indicated. In addition there are efferent vasomotor and secretory fibers. The afferent fibers of the stomach transmit nerve impulses that give rise to sensations of hunger, satiety, pain, and the like.

The book by Alvarez (1940) contains a good discussion of the extrinsic nerves of the digestive tract.

HUNGER CONTRACTIONS

That there is a relationship between hunger and certain types of stomach contractions has been established by the work of a number of investigators (Cannon, 1911; Carlson, 1916; Patterson, 1933). These movements, known as hunger contractions, may be recorded by the balloon-manometer method, or they may be studied by the roentgen ray. Hunger contractions of the stomach of the dog are illustrated

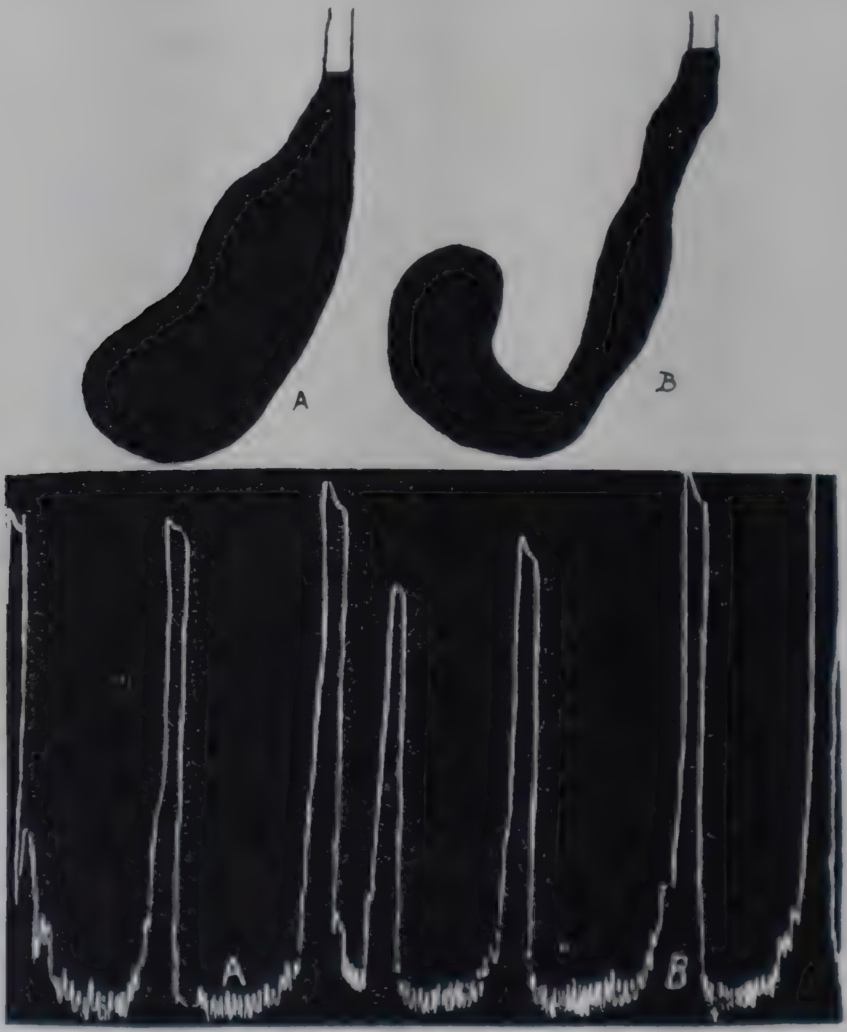


FIG. 81.—Hunger contractions of the stomach of a dog. The animal had been without food for 30 hours. The outlines at the top are of the bismuth-coated balloon in the stomach—A, between hunger contractions, and B, at the height of a hunger contraction. (From Carlson's *The Control of Hunger in Health and Disease*, The University of Chicago Press.)

in Fig. 81. It has been shown that hunger contractions are actual peristaltic waves traveling from the cardia to the pylorus. They therefore cover considerably more territory than do the ordinary peristaltic waves, which occur principally in the pyloric part. Hunger contractions may appear before the stomach has completely emptied itself. This is particularly true in herbivores. In the horse Schalk and Amadon (1921), using the balloon-manometer method, found that hunger manifests itself in the form of powerful contractions. These may begin as early as five hours after an ordinary meal, when the stomach still contains a good deal of food. Between hunger periods in this animal, there is an interval of relative quiescence, varying from fifteen minutes to an hour or more in different animals (Fig. 82).

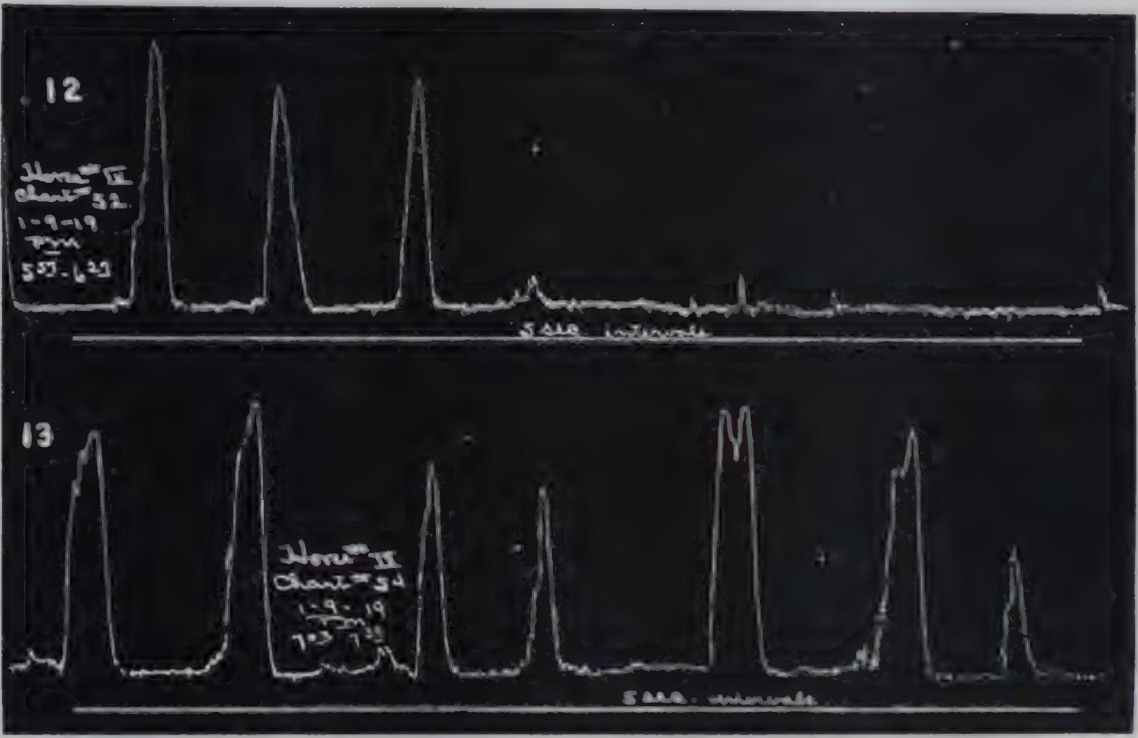


FIG. 82.—Hunger contractions of the stomach of a horse, with an intervening period of quiescence. Thirty-five minutes elapsed between the end of the upper tracing and the beginning of the lower. The animal was without food for 60 hours. (From Schalk and Amadon, *Journal of the American Veterinary Medical Association*, 1921, **59.**)

It has been shown that there is a relation between the blood sugar level and hunger contractions (Bulatao and Carlson). A decrease of blood sugar causes increased contractions, whereas glucose injections inhibit the strong tetanic contractions of hypoglycemia. Such a relation appears logical: when the blood sugar begins to decrease because of its usage in metabolism, there results a call for food via the gastric hunger mechanism. That chemical substances in the blood are concerned in hunger contractions is further indicated by the observation of Farrell and Ivy that a transplanted stomach pouch shows contractions during hunger contractions of the main stomach.

So-called hunger contractions are not the sole cause of the sensation of hunger. Dogs and people from whom the stomach has been completely removed show hunger. Probably chemical changes in the blood affecting nerve centers directly have something to do with hunger. Sensations reaching the brain from the small intestine or from the body at large may be concerned.

GASTRIC SENSATION

The question of gastric sensation resolves itself into the question of the extent to which nervous impulses from the stomach reach consciousness. Carlson and his associates (Carlson, 1916) made an extensive study of this problem on normal men and on a man with a gastric fistula. It is not possible to say to what extent their conclusions are applicable to animals, though it is probable that in a general way they apply to all higher species. Among the conclusions reached are the following: (1) The only physiological pains from the stomach are hunger pangs. All other pains of stomach mucosal origin are pathological. The normal mucosa in a normal subject can be pressed, squeezed until crushed, pricked, or cut, without causing pain. (2) Stimulation of the normal gastric mucosa does not produce touch sensation. (3) The stomach mucous membrane possesses warmth and cold receptors, but such receptors are more abundant, or are more readily stimulated, in the pharynx and esophagus.

The mucous membrane of the rumen and reticulum of the cow appears to be insensitive to touch and gentle pressure. Squeezing the reticulum in the hand, pulling on its floor, or pulling on the rumino-reticular fold appears to give rise to sensations. Strongly dilating the reticulo-omasal orifice appears to cause pain.

THIRST

Thirst is a sensation referred to the mucous membrane of the mouth and pharynx, especially that of the base of the tongue and of the palate. When a local anesthetic is applied to these regions, thirst is said to disappear as long as the anesthetic lasts. Physiological thirst may be relieved by water drinking and, according to some, by anything that excites a flow of saliva. This latter observation has been interpreted to mean that the sensation of thirst is due to dehydration of the oral and pharyngeal mucous membranes. Because the salivary glands regulate the amount of moisture bathing these regions, Cannon has advanced the hypothesis that these glands perform the important work of regulating the water intake of the body. When the water content of the blood falls, water passes into the blood from the various tissues including the salivary glands. Thus salivary secretion is diminished, the oral and pharyngeal mucous membranes become dry, and craving for water results. In this way the amount of the salivary secretion is believed to determine the water intake.

However, the work of Montgomery does not support the view that the salivary glands function in this way. Following the total removal of their salivary glands, the water intake of dogs was not increased, and the buccal mucous membrane remained in a healthy and moist condition. Furthermore it was shown that injections of atropine, which diminishes salivary secretion, caused no significant change in the water intake of normal dogs or dogs whose salivary glands had been removed; and that injections of pilocarpine, which increases salivary secretion, showed, in dogs following a period of water deprivation, no relief from thirst.

Adolph studied water drinking in dogs with esophageal fistulas, and in normal dogs, after they had been deprived of water. In both conditions the amount of water ingested was proportional to the deficit of water in the body. Actual ingestion of water following deprivation was very rapid, the deficit of water in the body being restored in a very short time.

The work of Bellows indicates that there are at least two factors in the alleviation of thirst. One of these operates from the mouth and pharynx, as indicated by the fact that sham-drinking gives temporary relief from thirst. It is suggested that repetitive muscular movement is concerned in the satisfaction attained by sham-drinking. The other factor in the relief of thirst is subpharyngeal in origin. Relief comes before absorption can be complete. Distention of parts of the alimentary tract might in some way inhibit thirst.

Bellows and Van Wagenen abolished by nerve transections the sense of taste, smell, or the sensations mediated by the trigeminal nerves in dogs, and found that water drinking was normal in amount.

The signal for water drinking in ordinary life seems to be a deficit of water in the body relative to other constituents. When the water deficit amounts to about 0.5 per cent of the body weight, water is drunk. The amount consumed is proportional to the deficit in the body at the time of drinking. Ingestion ceases before absorption has had time to occur (Robinson and Adolph).

Continuous records of water intake in normal dogs have been made by Gregersen (Fig. 83). It was found that most of the water ingested during a 24-hour period is taken within 2 to 5 hours after feeding, irrespective of the time of eating. Fasting greatly reduces the 24-hour intake of water.

VOMITING

Vomiting is the spasmodic ejection of the contents of the stomach through the esophagus and mouth. The act is not common to all species of animals. Herbivorous animals and rodents seldom or never vomit, whereas carnivores and omnivores (except those that are rodents) vomit readily. Various views have been advanced to explain why certain animals do not vomit. The uncommonness of vomiting in the horse has been attributed to such supposed hindrances as the distance of the stomach from the abdominal wall, the tightly closed cardia, and the constricted terminal part of the esophagus. But these factors are not present in all nonvomiting animals. Hence it has been held that the absence or rudimentary development of a vomiting center is the essential cause of the inability of many animals to vomit. Hatcher and Weiss, on the contrary, believe that the lack or poor development of a vomiting center is the effect, rather than the cause, of the absence of vomiting. The original significance of vomiting was probably to assist animals in combating poisons taken in with the food, and Hatcher and Weiss advanced the theory that rats and possibly other nonvomiting animals owe their inability to vomit to

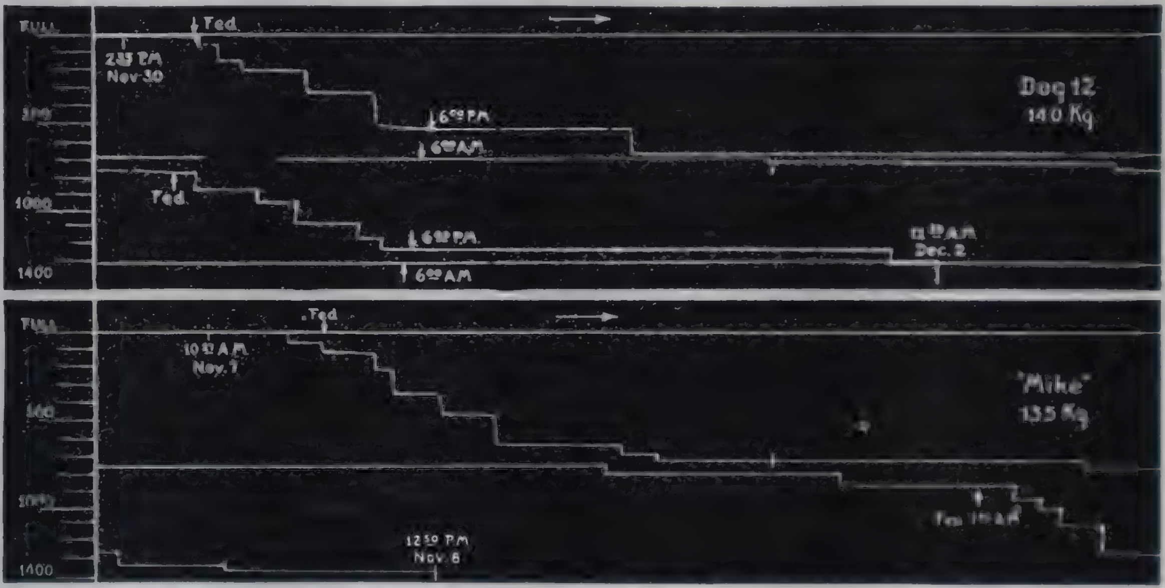


FIG. 83.—Records of water drinking by two normal dogs. A 12-hour period is covered by one excursion across the record. Note that most of the water drunk is taken within a few hours after feeding, regardless of when the food is given. The numbers at the left of the records are in cubic centimeters. (From Gregersen, *American Journal of Physiology,* 1932, **102**.)

the development of more effective means of combating poisoning, for example, selective absorption. Nausea, which is experienced also by animals that do not vomit, would stop the ingestion of poisonous food, and selective absorption would delay or prohibit its entry into the blood. Hence vomiting would not occur. This condition repeated in many successive generations might lead eventually to inability to vomit because of loss of sensitiveness of the nervous mechanisms controlling vomiting.

The Vomiting Act. The mechanism of vomiting has been comprehensively reviewed by Hatcher. His description of the typical act in the dog is the basis for many of the following statements. As a result of the reception of afferent nervous impulses, the vomiting center discharges efferent emetic impulses to the muscles concerned in vomiting. The pylorus and the pyloric part of the stomach contract firmly and the antrum pylori moderately. The fundus relaxes and the contents of the stomach are forced into this part. Antiperistalsis of the stomach may be present; however, it is of little consequence in vomiting. Salivary secretion is increased, respirations become deep and rapid, nausea is increased, chewing and swallowing movements are made. The material swallowed is saliva, usually mixed with air. The cardia opens and retching begins, this being described by Gold and Hatcher as consisting of a series of spasmodic, abortive respiratory movements with a closed glottis. The inspiratory phase of the movements consists of contraction of the thoracic muscles and the diaphragm together with expiratory spasmodic contraction of the abdominal muscles. The glottis remains closed until expulsion of the vomitus ceases. The first few retching movements drive some of the gastric contents into the esophagus. Near the last movement the cardia closes, the diaphragm relaxes, and a forceful contraction of the abdominal muscles drives the stomach against the diaphragm. The positive pressure so induced in the thorax and esophagus, aided by an active contraction of the muscular wall of the esophagus, drives some of its contents out through the mouth. The remainder of the vomitus passes back into the stomach. The whole chain of events may be repeated or quiescence may result.

The stomach is not essential to vomiting. This is indicated by the fact that completely gastrectomized dogs may vomit.

In the horse, as previously stated, vomiting is rare. When it does occur the ingesta, owing to the long soft palate, usually rush out through the nostrils. Vomiting in this animal is sometimes found to be associated with a ruptured stomach.

The Nervous Mechanism. Vomiting is a reflex act. A vomiting center has been located experimentally in the medulla oblongata in the sensory nucleus of the vagus (Hatcher and Weiss). This center exerts a correlating influence over the motor nuclei that normally control the muscles involved in vomiting. The efferent pathways to the numerous muscles—some striated, some nonstriated—are contained in the vagi and the spinal cord. Afferent fibers are present in a number of nerves and have receptors in diverse parts of the body. From such organs as the pharynx, stomach, duodenum, heart, uterus, kidney, bladder, brain, and semicircular canals, afferent impulses may pass to the vomiting center, stimulating it to action. It is well known that certain psychic states may cause nausea and vomiting.

An *emetic* is a drug that causes vomiting. Some emetics, as apomorphine and morphine, act on the vomiting center; others, as copper sulfate, zinc sulfate, and tartar emetic, act peripherally on receptors in the gastric mucosa; some others have both central and peripheral effects.

Chapter XIV

DIGESTION IN THE RUMINANT STOMACH

IN herbivorous animals it is essential that the alimentary canal have somewhere in its course a roomy compartment where the bulky, fibrous food can be delayed in its passage through the canal and undergo soaking and fermentation. This requirement in animals with simple stomachs is fulfilled in the cecum and colon; in ruminants, in the complex stomach especially the great chamber designated the rumen. Several lines of evidence indicate that the arrangement in the ruminant for the digestion of cellulose and other refractory components of the diet is superior to that in the nonruminant herbivores. Synthesis in the alimentary canal is also better developed in ruminants. These advantages are due mainly to the great size of the rumen.

ANATOMY OF THE RUMINANT STOMACH

The ruminant stomach, characterized anatomically by its great size and its division into several distinct compartments, appears to be an evolutionary modification of the simple stomach. Its capacity varies greatly with the age and size of the animal. According to Sisson (1914a), the capacity in cattle of medium size is 30 to 40 gallons, in large animals 40 to 60 gallons, in small animals 25 to 35 gallons.

The ruminant stomach is compound and consists of four compartments or divisions, designated as rumen, reticulum, omasum, and abomasum (Fig. 84). By some, each compartment is regarded as a separate stomach and is designated numerically, the rumen being known as the first stomach, the reticulum the second, etc. It is incorrect, however, to regard the ruminant as having more than one stomach. Again, because their mucous membranes are nonglandular and the epithelium is of the stratified squamous type, the rumen, reticulum, and omasum are sometimes regarded as esophageal dilatations. Embryological studies (Lewis) show that such a view is erroneous. These compartments develop from the embryonic stomach and not from the esophagus. The rumen, reticulum, and omasum may represent regions that lost their gastric glands while undergoing extensive phylogenetic modifications in size and form caused by the coarse, bulky character of the food

(Bensley). The relative size of the four compartments varies with the age of the animal. In the newborn calf the first three compartments are small. They develop as the animal grows and passes from a milk diet to one containing grain and roughage. According to Sisson (1914a), in the newborn calf the rumen and reticulum together are about one-half as large as the abomasum. In 10 to 12 weeks the abomasum is about one-half as large as the rumen and reticulum combined. During this time the omasum seems to be contracted and functionless. At four months of age the rumen and reticulum together are about four times as large as the omasum and abomasum together. At the age of about a year and a half, the four compartments have reached their permanent relative sizes, the rumen accounting for about 80 per cent of the stomach capacity, the reticulum 5 per cent, the omasum 7 to 8 per cent, and the abomasum 8 to 7 per cent.

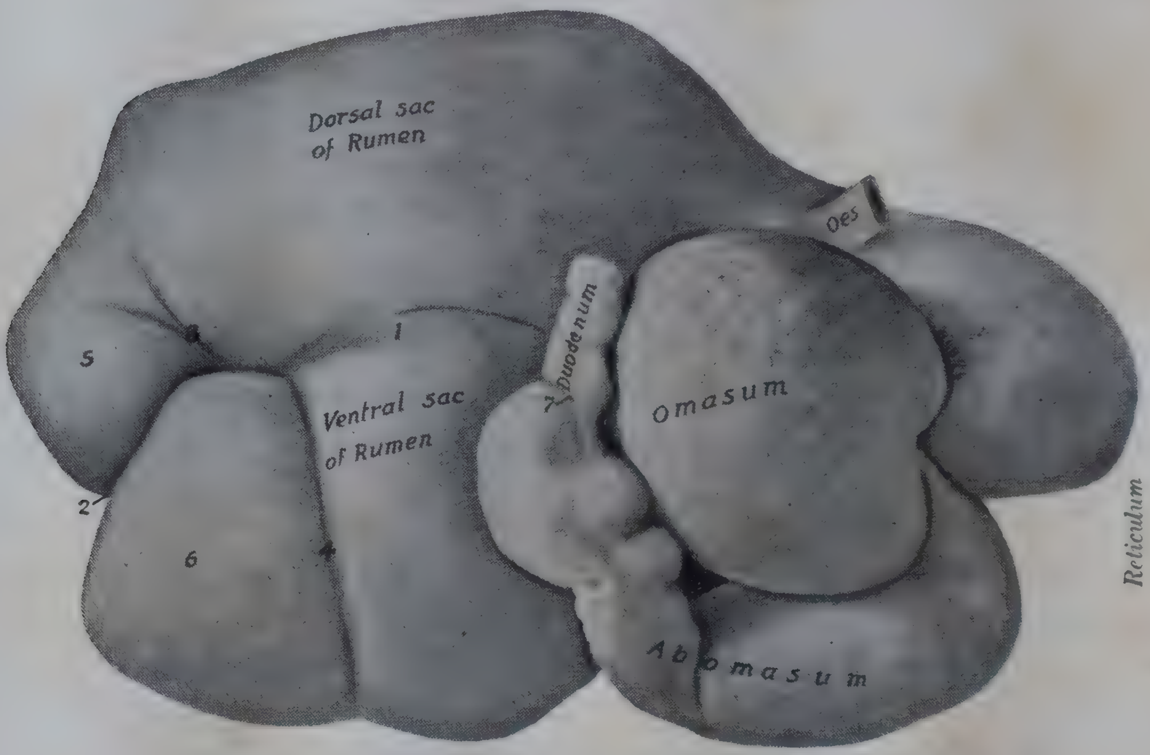


Fig. 84.—The stomach of the ox (right view). (From Sisson's *Anatomy;* copyright—W. B. Saunders Company.)

The rumen presents dorsal and ventral sacs, which freely communicate with each other through a large opening surrounded by muscular pillars. The anterior and posterior pillars are especially well developed and powerful. There is also a pair each of longitudinal, dorsal coronary, and ventral coronary pillars. The rumen communicates freely with the reticulum over the ruminoreticular fold. From the cardia to the reticulo-omasal orifice extends the peculiar esophageal or reticular groove. In the ox it is 7 or 8 inches in length. The mucous membrane of the rumen is nonglandular and in most situations is covered with papillae, which are especially well developed in the ventral sac.

The reticulum lies against the diaphragm and liver. It is small and somewhat flask-shaped. It communicates with the rumen over the ruminoreticular fold and with the omasum through the comparatively small reticulo-omasal orifice. Its base is below the inlet and the outlet. The mucous membrane is nonglandular and is thrown into folds, so that it resembles a honeycomb.

The omasum is somewhat globe-shaped. It communicates with the reticulum through the reticulo-omasal orifice and with the abomasum through the large omaso-abomasal orifice. The sulcus omasi is a groove extending mainly downward from the inlet to the outlet. Newer anatomical studies on the ox (Sisson, 1923a) show that the direction of the sulcus is much more nearly vertical than was formerly believed. The interior of the omasum presents numerous folds or laminae. They are attached to the wall of the organ except in the region of the sulcus. As regards length, the folds can be grouped into about five orders. The longest folds extend almost across the organ; the smallest are mere ridges; the others are of intervening lengths. The leaves have some muscular tissue in their structure and are studded with numerous papillae covered with cornified epithelium. Certain ruminants (Tragulidae and Moschidae) have no omasum; that of the sheep and goat is not well developed.

The abomasum is the glandular compartment of the ruminant stomach. It communicates with the omasum and, through the pylorus, with the duodenum. It is divided by a constriction into two portions, the fundic and pyloric regions. Fundic and pyloric glands, respectively, are found in these parts. The mucous membrane of the former region is thrown into about 12 large spiral folds. The mucous membrane of the pyloric region is similar in appearance to that of the pyloric region of other animals.

MECHANICAL FACTORS

Many aspects of the physiology of the ruminant stomach, particularly the mechanical factors, can be studied by means of a fistula of the rumen through the left flank (Fig. 85). Numerous investigators have used this method. In small ruminants the roentgen ray has been utilized effectively (Czepa and Stigler; Magee, 1932; Phillipson, 1939; Watson and Jarrett). The open-abdomen, saline-bath method has been applied successfully to sheep (Dukes and Sampson, 1937). The best results by this method were obtained with the abomasum.

Rumen and Reticulum. It is agreed by most observers that anything swallowed in a *normal* manner, in the mature ruminant, goes to the anterior dorsal sac of the rumen. Some of the heavier food soon finds its way into the reticulum. The lighter ingesta, together with much of the heavier, collect in the rumen, gradually filling it but not to the top. Usually there is a collection of gas above the food mass.

The physical character of the swallowed bolus and of the rumen contents have been studied in the cow by means of the fistula method (Schalk and Amadon). The form, weight, and consistency of the bolus vary a good deal, depending upon the kind of food consumed. Roughage gives rise to a firm, oval bolus; cured hay boluses, because of their low moisture content, float in water. After hay boluses have been in the rumen awhile, they lose their identity, and the material of which they are composed becomes heavier and softer because of the prolonged maceration that it undergoes. Boluses of most concentrates are heavier than those of roughages. The average weight of whole-oat boluses is 140 gm.; ground-food boluses, 101 gm.; whole-corn boluses, 81 gm.; hay boluses, 85 gm. The average weight of boluses of the four kinds of foods is 101 gm.

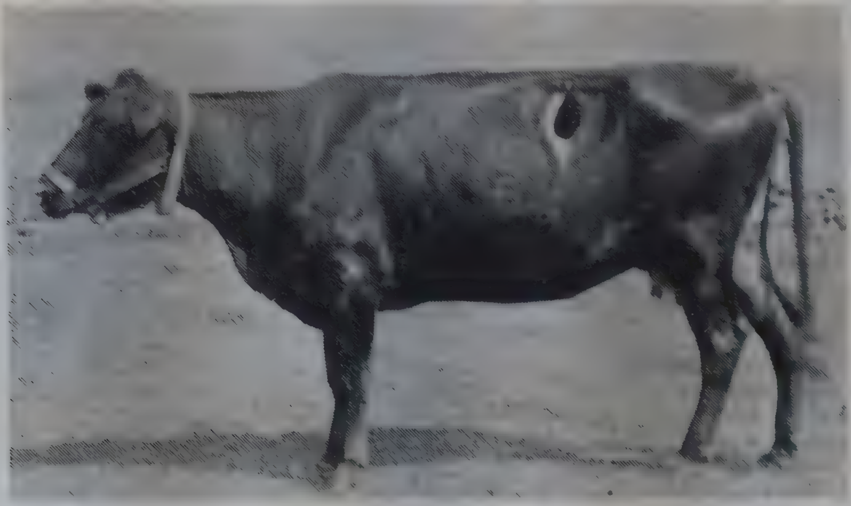


FIG. 85.—Rumen fistula. The photograph was taken several months after the operation. Note the excellent condition of the animal. (From Schalk and Amadon, *North Dakota Agricultural Experimental Station Bull.* 216, 1928.)

In full-fed cattle there may be little or no free liquid in the rumen. In fasted animals, on the other hand, much free liquid is present (Nevens). This is found principally in the ventral sac, the moist ingesta of the dorsal sac floating on this liquid. Ross has emphasized that in nonfasted sheep the ruminal contents are nearly always solid or semisolid in consistency, in sheep fasted for 24 hours the ruminal contents are of a semifluid or fluid nature, and in animals fasted 40 to 48 hours of a watery consistency.

The rumen requires a large amount of water for its normal functioning. This explains in part the enormous salivary secretion of ruminants and indicates that these animals should have water ad libitum.

The reticulum may be regarded as an anterior continuation of the rumen, with which it freely communicates over the ruminoreticular fold. The reticular content is made up of liquids and suspended solids. The more solid ingesta of the rumen are kept from entering and choking up the reticulum by the ruminoreticular fold, which acts as a dam between the two organs.

At fairly regular intervals throughout the day, portions of the ruminal and reticular contents are returned to the mouth for remastication and reinsalivation. During their sojourn in the rumen the ingesta are subjected to energetic mixing, kneading, and churning because of rumen and reticular motility.

Movements. The movements of the rumen and reticulum are very closely associated. The normal sequence of their motility in the nonruminating ox is about as follows (Schalk and Amadon, 1928):

The reticulum undergoes a sharp contraction followed almost immediately by another similar contraction. As a result, liquid material is thrown into the rumen. Before the second reticular contraction is complete, however, the anterior pillar of the rumen begins to contract, forming a barrier to the second reticular outflow. Material forced out by this second contraction is therefore largely retained in the anterior dorsal sac of the rumen. The wave of rumen contraction, begun at the anterior pillar, proceeds backward involving practically simultaneously the longitudinal pillars, the posterior pillar, the dorsal coronary pillars, and the intervening rumen wall. As these structures relax, the ventral coronary pillars and the musculature of the ventral sac go into contraction. This forces ingesta forward and upward into the anterior dorsal region of the rumen. Following the primary wave of contraction there is a secondary wave, which involves the rumen only. It begins with a contraction of the anterior pillar and then proceeds backward after the manner of the primary wave.

Schwarte studied rumen contractions by palpation in a large number of cows under conditions of eating, rumination, and rest (noneating and nonrumination) and obtained average frequencies as follows:

During eating	2.8 rumen contractions per minute
During rumination	2.3 rumen contractions per minute
During rest	1.8 rumen contractions per minute

The movements of the reticulum and rumen, especially of the latter, are thus seen to be very complex. They cause many variations of pressure, both positive and negative, and perpetual rotation of the ingesta, which results in effective maceration.

The pumplike action of the reticulum causes a flow of liquid into and out of the rumen, the significance of the flow being: (1) To direct ingesta into the rumen. If the newly arrived bolus is composed of lightweight material, such as cured hay, it is carried on the crest of a reticular outflow into the rumen. There is less tendency for the heavier ingesta to be carried into the posterior part of the rumen when the rumen is not well filled; consequently when the reticulum relaxes, some of this material may be drawn at once into its cavity. (2) To regulate the passage of ingesta from the rumen to the omasum or abomasum. Ruminated material, because of its high moisture content and specific gravity, soon finds its way into the reticulum. Ingesta entering this organ following rumination soon pass into the omasum or abomasum. (3) To supply moisture to the rumen contents. (4) To assist in regurgitation. To accomplish this another reticular contraction, occurring just prior to regurgitation, is introduced. Part of the regurgitated material is derived from the reticulum and part from the rumen.

Sounds. During contraction the rumen produces sounds which are readily heard by auscultation over a wide area. Reticular contraction also produces sounds but they are not always readily heard. Auscultation over several regions will usually reveal them, but they are best heard ventrally over the seventh rib, on the left side. They are described as chafing sounds (Lagerlöf).

Reticuloruminal Motility in Sheep. This has been studied by Phillipson (1939) by means of rumen fistulas and the roentgen ray. The cycle of reticuloruminal motility usually occurs at intervals of 30 to 70 seconds. Reticular contraction occurs in two stages, usually followed by two or four contractions of the rumen. Variations were noted both in the contractions of the reticulum and of the rumen.

Quin and co-workers have made studies on rumen motility in sheep by means of the rumen fistula. They noted that the rumen movements may vary considerably from any pattern temporarily established. The degree of relaxation of the rumen between contractions is indicated by the considerable negativity of intraruminal pressure (-5 to -15 mm. H_2O) that may develop. When contraction is at its height the average intraruminal pressure is 70 mm. H_2O. Feeding accelerates the movements. A fast as long as three or four days usually causes no definite change in the rate of rumen contraction, although the waves may become smaller. After a fast of three or four days all movements may disappear. The sight of water and actual drinking were without significant effect on rumen motility.

Although reticuloruminal motility in the sheep is subject to greater normal variability than in the cow, the sequence of events is essentially the same in all ruminants (cow, sheep, goat).

Esophageal Groove and the Course of Liquids. The esophageal groove, known also as the reticular groove, begins at the cardia and extends to the reticulo-omasal orifice. For a long time it was supposed, largely on the basis of anatomical studies, that the esophageal groove functioned to convey liquid and semiliquid ingesta from the cardia directly to the reticulo-omasal orifice without their having to traverse the rumen and reticulum. Such a view of the function of the groove *in the mature animal* apparently cannot be held at the present time. Direct examination of the groove in mature cattle with rumen fistulas shows that little or no food material traverses the groove (Schalk and Amadon, 1928; Dukes). About the only thing that can be detected is the passage of mucus, doubtless derived in part from the saliva which runs down the esophagus without exciting an actual deglutition, and in part from the secretion of the esophageal glands.

The Course of Liquids in Young Ruminants. In young ruminants the esophageal groove may function, by reflex closure, as a conduit for milk or water on its way from the esophagus to the reticulo-omasal orifice. The reflex by which the groove is closed has been thought to diminish in sharpness or to disappear as the animal matures. Behavior patterns, psychological factors, and conditioned reflexes probably are important in the reflex closure of the esophageal groove. The age of the animal may be a secondary factor, but the shift from the "sucking pattern" of behavior to the "thirst pattern" is believed to be of significance. The reflex is evoked as a part of the sucking pattern of behavior but not as a part of the thirst pattern (Watson). After weaning the only liquid normally consumed by the ruminant is water to quench thirst, and the drinking of water does not evoke the reflex.

By observations made at autopsy and through rumen fistulas, Wise and Anderson studied the course of liquids drunk by calves from pails and through nipples. The ages of the calves ranged from a few days to nearly six months. Great variations in the responses of the calves were noted. When milk was drunk from an open pail, small amounts often entered the rumen. When milk was taken through a nipple, it never entered the rumen in significant amounts. Water drunk from a pail entered the rumen in large amounts. Water sucked through a nipple occasionally entered the rumen in small amounts. The position of the head and neck of the calf while consuming milk was of no significance in determining the course of the milk through the stomach (Wise, Anderson, and Miller).

The Effect of Various Chemicals on the Reflex Closure of the Esophageal Groove. In young healthy cattle up to two years old, the reflex can be evoked, according to Wester, by the administration of various chemical substances in solution, including sodium salts, especially sodium chloride and sodium bicarbonate, and sugar. This investigator therefore recommended the giving of groove-closing substances prior to the administration of drugs not intended for the rumen or reticulum but for the abomasum. Wester's work was done on cattle. In South Africa, Mönnig and Quin have studied the possibility of dosing into the abomasum of sheep, using Wester's work as the basis of their experiments. When solutions of sodium salts were administered in an effort to produce reflex closure of the groove, the results were of such a nature that practically no conclusions could be drawn. However, when a solution of copper sulfate was used, reflex closure of the groove was obtained, so that drugs subsequently given passed into the abomasum. The reflex was evoked immediately after the stimulant came in contact with the pharyngeal mucous membrane, and the groove remained closed for 15 seconds or longer. Probably the mucous membrane of the pharynx contains receptors for initiating the reflex. In Australia, Ross, working with sheep, confirmed the groove-closing properties of copper sulfate. The researches of Quin and van der Wath suggest considerable individual variations in the response of the esophageal groove of sheep to the administration of copper sulfate. Watson and Jarrett made an extensive study of the effects of copper salts, especially copper sulfate, on the course taken by liquids entering the stomach of the sheep. The copper salt was given in solution and the liquid administered afterward was a water–barium-sulfate suspension. The course of the suspension was followed by means of the roentgen ray. In most animals the suspension passed to the abomasum when given shortly after the dose of copper sulfate, but in some animals irregular results were obtained. The reflex response of the esophageal groove usually occurred within 8 seconds after the copper sulfate was given. The response usually lasted more than a minute and in some cases it persisted for more than 11 minutes. The evidence indicated that the receptors are located in the mucous membrane of the mouth, pharynx, and possibly the upper part of the esophagus. The cupric ions were thought to be the stimuli. Ten cubic centimeters of 0.40 M (10 per cent) copper sulfate administered into the mouth gave a satisfactory reflex response. Other copper salts were tried and the responses obtained were similar to those obtained with copper sulfate.

Omasum. By means of the roentgen ray, Czepa and Stigler made a careful study of the movements of the stomach of the goat. They were unable by this means (confirmed by Magee, 1932) to detect any omasal contraction. However, upon examining the omasum in the recently killed animal its contraction was found to be peristaltic in type. Phillipson (1939) comments on the difficulty in studying the omasum radiographically. In open-abdomen, saline-bath experiments in sheep, the omasum does not show spontaneous contractions. According to Wester the parts of the omasum contract in the following order: the neck, the vestibule, the body. As a result of the contraction of the omasum its contents are subjected to considerable pressure, and some of them are passed on into the abomasum. Quick relaxation follows the contraction.

Schalk and Amadon (1928) studied omasal contractions by inserting a balloon into the organ through a rumen fistula and the reticulo-omasal orifice. The contractions were found to be slow, sluggish, and often superimposed on strong tonus waves. At times there is negative pressure in the organ. It is possible that this is concerned in the passage of ingesta from the reticulum to the omasum. Contraction of the omasum appears to be co-ordinated to some extent with that of the first two stomach compartments.

Semiliquid material from the reticulum enters the omasum by the reticulo-omasal orifice. The more fluid portions probably pass directly into the abomasum via the sulcus omasi, which runs nearly vertically. The solids are largely held back, being caught between the numerous papillated leaves. A good deal of the moisture mixed with the solid material is then probably squeezed out by repeated omasal contractions. Some of the liquid so released probably undergoes absorption in the omasum. Part of it doubtless passes on into the abomasum.

There is no doubt that one of the functions of the omasum is to grind or triturate food materials entering it (Ewing and Wright; Becker; Trautmann and Schmitt). But knowledge of the extent of the grinding is uncertain, and the mechanism by which it is accomplished is largely unknown. It was once believed that ingesta entering the spaces between the omasal laminae were triturated by simultaneous contraction and relaxation of adjacent leaves. There is no direct evidence to support this view. Wester, in extensive studies of the ruminant stomach, found no facts to substantiate it. By palpation of the leaves through the reticulo-omasal orifice, Dukes found no evidence of their contraction. Histological studies of the omasal laminae by Favilli did not suggest that they are important comminuting devices. It seems probable that omasal grinding, to the extent that it occurs, is effected less by specific motility of the laminae than by general contractions of the whole organ.

That the function of the omasum can be largely dispensed with is suggested by the work of Trautmann and Schmitt who in young goats produced both a reticulo-abomasal and a rumino-abomasal stoma, thus permitting food to pass from the first two compartments into the abomasum without having to traverse the omasum. Such animals grew well and remained in good health. At autopsy months later it was found that the omasum was much smaller than in normal animals.

It has been observed in acute experiments in sheep (Dukes and Sampson, 1937) that stimulation of the vagus nerve, although causing strong contraction of the wall of the omasum, causes no apparent tightening of the leaves. This evidence tends to show that the motility of the leaves, if they possess any of consequence, is not controlled by the nervous factors that govern wall motility.

Abomasum. In open-abdomen, saline-bath experiments in sheep the abomasum shows good motor activity (Dukes and Sampson, 1937). The contractions resemble those seen in the simple stomach. The fundus is usually quiet. The body shows numerous contractions and relaxations. (These are apparently missed in radiological studies of abomasal motility). The pyloric part shows peristaltic waves. At times several may be traveling simultaneously. They pass right up to the pylorus, that is, they do not give way to systoles and diastoles of the pyloric part.

The Rate of Passage of Food Residues. The rate of passage of food residues through the stomach compartments of steers has been studied (Ewing and Wright) by a method based upon a digestion trial and a subsequent slaughter test, with these average results: rumen and reticulum, 61 hours; omasum, 7.9 hours; abomasum, 2.8 hours.

McAnally and Phillipson state that Usuelli gave stained oats to cattle that were otherwise normally fed and determined the time required for the oats to disappear from the rumen. Samples of rumen ingesta were removed periodically by stomach tube for examination. In two days 50 per cent of the stained oats had disappeared from the rumen. Some oats remained in the rumen for 7 days.

Accumulation of Foreign Matter in the Ruminant Stomach. It is well known that cattle may consume a good deal of foreign matter with their food and that this may be retained in the stomach, sometimes causing serious injury to its wall and to adjacent structures. Thus traumatic gastritis, traumatic pericarditis, or other traumatic inflammation can develop. It is therefore of interest to know in which compartments the foreign matter tends to collect, and this question has been studied by Nevens on dairy cows (14 animals). The reticulum and the abomasum were found to be the principal places of accumulation. The foreign matter in the reticulum was mostly nails, wire, glass, and sand, whereas that in the abomasum was chiefly small pebbles and cinders. Only a small amount of foreign matter was recovered from the rumen, and none from the omasum and intestine.

Because the ingesta in the reticulum are liquid, heavy foreign matter entering this organ will tend to settle out. Because the inlet and outlet of the reticulum are well above the fundus, heavy foreign matter will be expelled from the reticulum with difficulty. The vigorous contractions characteristic of the reticulum increase the liability to trauma from foreign bodies.

Induced Traumatic Gastritis. Working through rumen fistulas, Dougherty (1939) produced traumatic gastritis in cows by inserting foreign bodies (wire) through the wall of the reticulum so that they penetrated the peritoneal cavity. Contractions of the rumen decreased as early as two hours after the foreign bodies were introduced. Changes in the blood leucocyte picture were also observed (p. 45).

The Nervous Control of the Ruminant Stomach. The movements of the ruminant stomach, like those of the simple stomach, are automatic; this applies to all compartments. The vagus is the motor nerve of the four compartments. This can be shown by stimulation of the nerve in the cervical region, whereupon strong contraction of the stomach takes place. In calves stimulation of "the vagus nerve resulted in closure of the open relaxed esophageal groove and in marked motility of the rumen. Relaxing and subsequent opening of the groove followed in a few seconds after the cessation of the stimulation" (Wise, Anderson, and Miller).

The sympathetic (splanchnic) nerves are inhibitory to the ruminant stomach. This is evidenced by injections of adrenaline, which stimulates sympathetic nerve terminations. Magee (1932) observed, by means of the roentgen ray, that injections of adrenaline caused slowing and weakening of contractions of the reticulum. Dougherty (1942), working with cows having rumen fistulas, found that injections of adrenaline depressed rumen motility.

The Effect of Drugs on Rumen Motility. Rumen motility may be diminished in a number of pathological conditions. Overloading of the rumen with food and overdistention of the rumen with gas are common causes of depressed motility. Drugs promoting rumen motility are known as ruminatorics.

Several recent articles on the effect of drugs on the motility of the rumen have appeared (Quin and van der Wath; Dougherty, 1942; Amadon). A study of these reports makes it evident that much more research work needs to be done on this important subject before knowledge in this field can be considered as satisfactory. In general it may be said that the vagomimetic substances tend to promote rumen motility, but exceptions have been noted. With some drugs the dose is a factor which determines its effect on the rumen. Atropine and adrenaline depress rumen motility. Copper sulfate solution dosed on the back of the tongue causes acceleration of rumen movements. In some animals the increased motility occurs immediately, whereas in others a short period of inhibition precedes the stimulation. Insufflation of oxygen into the rumen has a stimulating effect on rumen motility (Dougherty, 1942). For further details of the drug actions the original articles should be consulted.

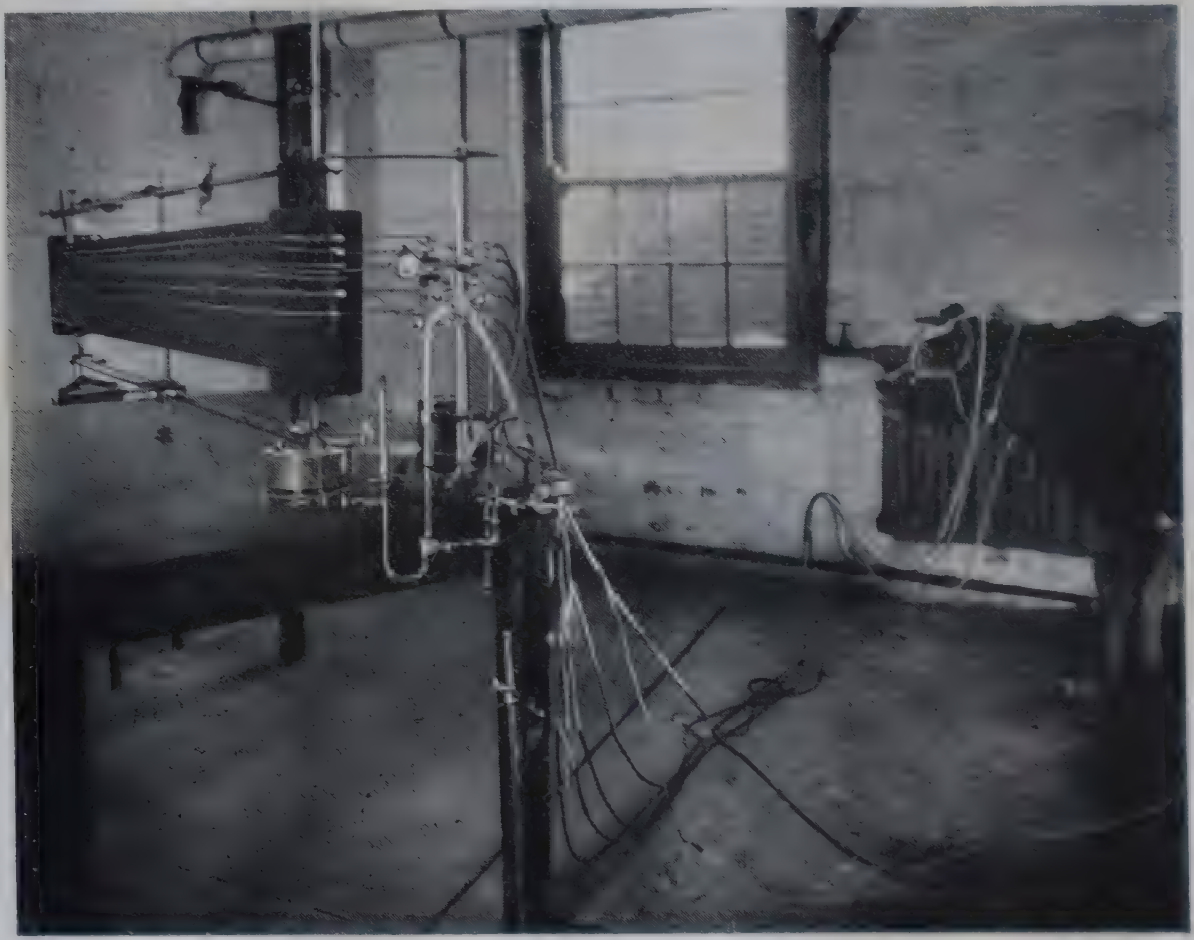


FIG. 86.—Arrangement of apparatus (tambours, bromoform manometer, kymograph, etc.) and subject for a study of the mechanism of regurgitation. A part of a tracing made in this way is shown in Fig. 87. (Bergman and Dukes.)

Rumination. Rumination embraces those mechanical factors of digestion whereby food in the stomach is regurgitated, remasticated, reinsalivated, and reswallowed. These four phases, together with a slight pause after reswallowing, may be said to make up a *cycle of rumination*. In its true sense rumination is confined to ruminants. These animals consume their food hurriedly and with little mastication; in the capacious rumen the food is stored to await rumination. While in the rumen it undergoes thorough mixing, maceration, and fermentation. At intervals portions are returned to the mouth for remastication and reinsalivation.

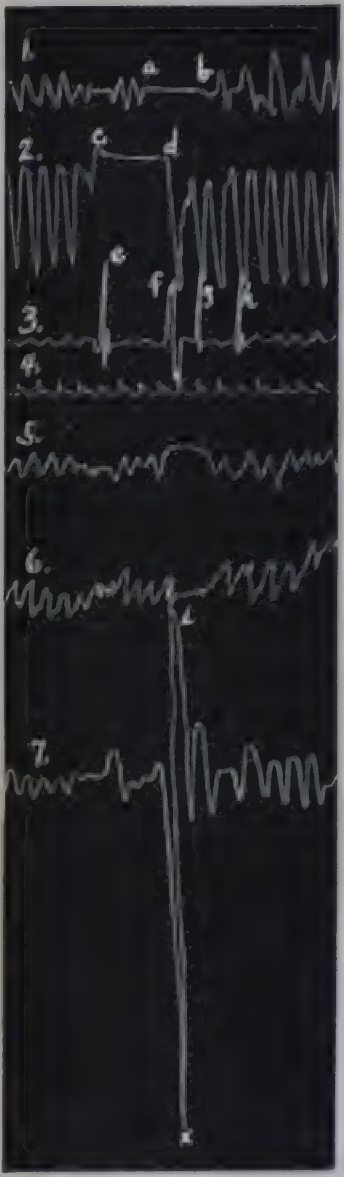


FIG. 87 (right).—Tracings to show the mechanism of regurgitation in rumination. The writing points were vertically placed. The cow regurgitated at x. 1. Movements of air in the nostrils. Note closure of the glottis from a to b. 2. Movements of the jaw in mastication. Note the pause, cd. 3. Movements of boluses in the cervical part of the esophagus: e, the masticated bolus; f, the regurgitated bolus; g, h, the swallowed liquid pressed out of the regurgitated bolus. 4. Time tracing showing 1-second intervals. 5. Movements of the thoracic wall. 6. Rectal pressure. Note that it is not elevated during regurgitation. 7. Pressure changes in the trachea. Note the sharp fall coincident with regurgitation. The rise of pressure at i is due in part to the momentum of the liquid (bromoform) used in the recording manometer and doubtless in part to an increase of intrapulmonic pressure due to the rebound of the thoracic wall. (Bergman and Dukes.)

Regurgitation. The food returned to the mouth doubtless comes in part from the rumen and in part from the reticulum. The regurgitated mass is highly mixed with liquid, the material in the region of the cardia and in the reticulum being of such consistency that it can readily enter the esophagus. The entrance of the ingesta (which for convenience may be called the bolus, although there is no definite bolus formation) into the esophagus is accomplished by an inspiratory effort with a closed glottis. This effort causes a sharp drop in intrapulmonic, intrathoracic, and intraesophageal pressures. The pressure in the rumen being higher, the semiliquid food in the region of the cardia is aspirated through the cardia, which is now relaxed, into the dilated terminal part of the esophagus. Having entered the esophagus, the food is carried quickly to the mouth. Reverse peristalsis probably plays an important part in its upward passage, though the momentum of the ingesta as they enter the esophagus and the elevation of pressure in the esophagus due to the sudden rebound of the distended thorax are doubtless factors. This view of the mechanism of regurgitation was investigated and confirmed years ago by Toussaint, for the ox and sheep, and more recently by Bergman and Dukes (1926), for the ox (Figs. 86 to 89). In the work of Bergman and Dukes negative pressure in the lungs was demonstrated (Fig. 87, 7) by connecting the interior of the trachea with a bromoform manometer or a tambour arranged to write on a kymograph. Owing to the thin-walled, capacious esophagus of the ruminant, negative pressure in the lungs, and hence in the thorax, should readily give rise to negative pressure in the thoracic part of the esophagus. That such actually is the case was demonstrated by direct examination of the region of the cardia in the ruminating animal. The examination was made by inserting the hand and arm through a rumen fistula in the left flank. Negative pressure could be felt at the cardia at the instant of regurgitation.

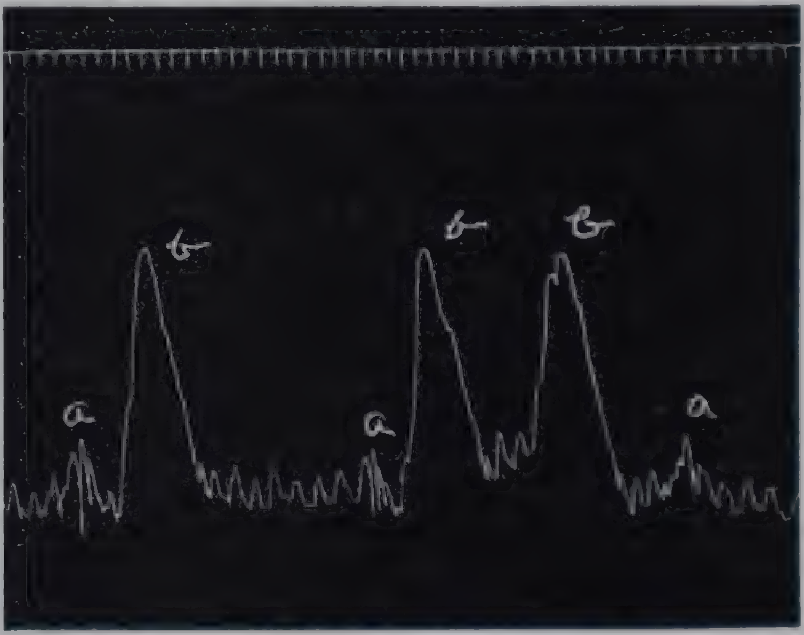


FIG. 88.—Tracing from a cow to show the condition of intraruminal pressure during rumination: *a*, regurgitation; *b*, contraction of the rumen. The other waves are caused by the respiratory movements. Note that contraction of the rumen follows regurgitation but does not coincide with it. The time tracing shows intervals of 2 seconds. (Bergman and Dukes.)

Direct examination seems to show that the esophageal groove plays no part in regurgitation, thus confirming Colin's conclusion. Colin years ago showed, by suturing together the lips of the esophageal groove, that it is not concerned in regurgitation, for the animals ruminated successfully afterward. It has been urged that contraction of the rumen wall is concerned in regurgitation by forcing ingesta into the esophagus. Graphic records and direct observation of the activity of the rumen show that this is not the case; the rumen does not contract during regurgitation (Fig. 88). Furthermore, the great rapidity of regurgitation makes it evident that it is carried out fundamentally by skeletal muscle contraction; the contraction of smooth muscle is too slow. The share played by the reticulum in regurgitation is not fully known. Flourens showed years ago that it probably is not essential by an experiment in a sheep in which he cut away the bottom of the reticulum and sutured the resulting rim to the floor of the abdomen. The animal ruminated afterward. Modern work also seems to show that the reticulum is not essential in regurgitation, at least from the standpoint of its motility. Graphic records show that the reticulum contracts just before, but not simultaneously with, regurgitation (Fig. 89). The function of this extra contraction appears to be to flood the region of the cardia with liquid and semiliquid ingesta just before regurgitation. The entrance of more solid ingesta into the esophagus is thereby facilitated. The abdominal muscles have been credited with undergoing contraction at the instant of regurgitation, thus assisting in the act. However, if an elevation of rectal pressure can be regarded as an indication of effective contraction of the abdominal muscles, it may be concluded that such contraction does not occur, for observations show that rectal pressure is not elevated at the time of regurgitation (Fig. 87, *6*).

It appears, therefore, that in regurgitation the entrance of food

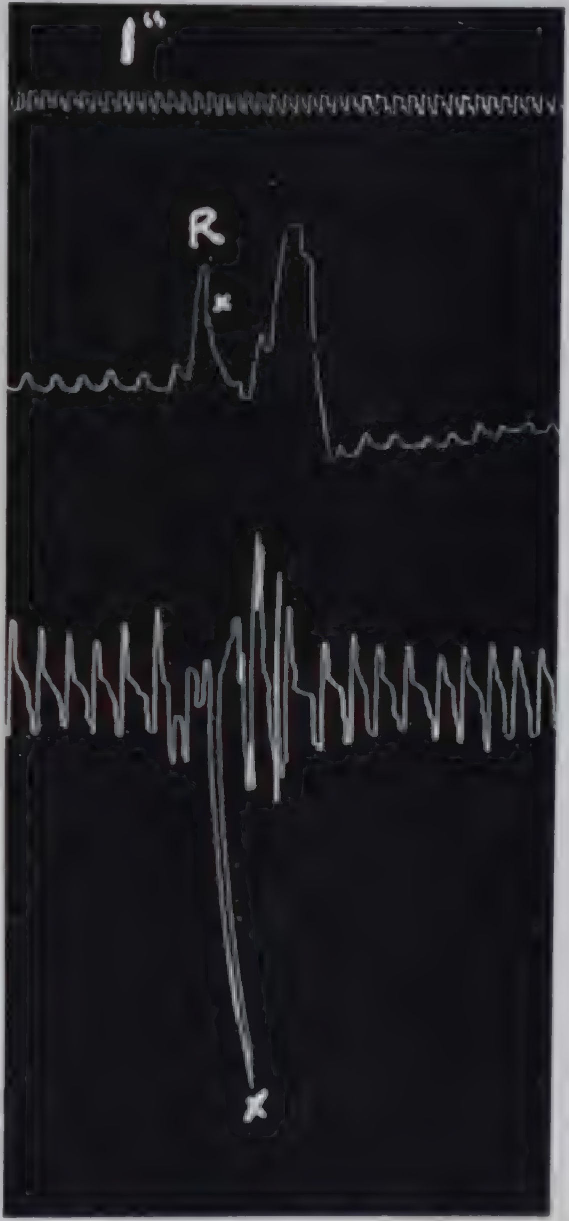


FIG. 89.—Tracings from a calf to show the temporal relation of the first reticular contraction (R) to regurgitation (x). The upper curve shows contractions of the reticulum and the anterior part of the rumen; the lower curve shows intratracheal pressure. The calf regurgitated at *x*, but it is evident that the reticulum had already contracted. The writing points were vertically placed. (Bergman and Dukes.)

into the esophagus is brought about by intraesophageal negative pressure due to an inspiratory effort with a closed glottis, the esophageal groove, rumen, abdominal muscles, and reticulum playing no direct part in the process.

Roentgen-ray studies on ruminating animals offer support to several phases of the theory of regurgitation expressed above.

Unilateral pneumothorax (goat) is reported to prevent regurgitation, although repeated attempts are made to accomplish the act. Ruminants with an opening into the trachea regurgitate with difficulty (Krzywanek).

The rate of passage of the bolus up the esophagus is about 1.4 meters per second.

The Nature of the Regurgitated Bolus. The water content of the bolus as it passes into the esophagus is great, and this must be so, otherwise the entrance of the bolus into the esophagus would be difficult or impossible. The studies of Schalk and Amadon on the nature of the regurgitated bolus in cattle indicate that it is composed mainly of roughage. Grains form a part of the bolus only to the limited extent that they are caught in the spaces of the roughage. It has been shown (Schalk and Amadon, 1928; Kick, Gerlaugh, and Schalk) that a large percentage of corn kernels is uncrushed during the mastication of eating. Since the kernels are remasticated only to a limited extent, it follows that many must pass intact through the animal when whole corn is fed and appear in the feces.

Remastication and Reinsalivation. The bolus passes into the mouth and remastication begins. This process is accompanied by reinsalivation. During the time occupied by the first few jaw movements, the animal swallows, in two gulps, much of the liquid that accompanied the bolus to the mouth; this material returns to the rumen. The remastication is thorough and deliberate, differing markedly from the mastication of eating. Fuller found, for example, that cows when eating grain and silage made jaw movements at an average rate of 94 per minute and when eating hay, at an average rate of 78 per minute, whereas when ruminating the average rate was only 55 per minute. Ewing and Wright in a study of the extent of comminution in different parts of the alimentary canal of steers found that more than half the comminution with average rations takes place as a result of mastication, including the remastication.

Reinsalivation differs from the insalivation of eating mainly in the fact that the submaxillary glands are practically inactive.

Redeglutition. This act differs in no significant feature from the deglutition of eating. The reswallowed food returns to the rumen. During remastication the bolus grows in size owing to the addition of saliva to it. Consequently, before the end of the mastication time a part of the bolus is usually swallowed, chewing being continued without interruption until the rest is swallowed. The rate of passage of the bolus down the esophagus is about 1.3 meters per second and is therefore practically the same as its rate of passage up.

The Course of the Ruminated Bolus. The ruminated bolus when swallowed returns to the rumen. It was formerly widely believed that it passed down the esophageal groove to the omasum or abomasum. There is convincing evidence that such is not the case in mature cattle. Direct examination of the groove in the ruminating animal reveals that no food of any consequence passes along it (Schalk and Amadon, 1928; Dukes). The questions now arise why the bolus just swallowed is not again returned to the mouth at the next regurgitation and how and when it passes to the omasum and abomasum. Two factors are probably concerned in insuring the removal of the ruminated bolus from the region of the cardia: its high specific gravity and an additional reticular contraction, the one that precedes the next regurgitation. These factors, and general reticular motility, cause most of the ruminated food soon to enter the reticulum. Thence it passes quickly to the other compartments. Negative pressure during omasal relaxation probably helps. A small amount of ruminated food makes the complete circuit of the rumen, and it is probable that a small amount is submitted to a second rumination.

Time Spent in Rumination. The total time spent daily in rumination varies considerably in different animals and with different rations. Results obtained by Fuller on dairy cows kept under modern herd conditions show an average daily rumination time of a little more than 8 hours. The minimum time is approximately 7 hours; the maximum, approximately 10.5 hours. Schalk and Amadon (1928) found an average rumination time of a little less than 7 hours. Bergman and Dukes (1925) have reported similar results. Limited observations suggest that cattle at pasture spend about the same amount of time in rumination as the foregoing.

Cut hay when fed to steers causes no reduction in the daily rumination time as compared with whole hay. Ground hay requires less rumination time. Grinding shelled corn for steers causes no reduction in the rumination time. The proportion of grain and roughage in the ration influences the rumination time. With a ration containing no roughage, the rumination time (steer) has been found to be only 4.5

per cent of the daily time; with a ration of hay alone, 36 per cent of the daily time. When the ration contains no roughage, rumination is slow and listless (Kick and co-workers).

The periods of rumination are remarkably evenly distributed throughout the 24 hours; no time of day seems to be especially preferred (Fig. 90). From the results of Fuller, and Bergman and Dukes, it appears that 14 is about the average number of rumination periods in 24 hours. The duration of periods varies from a few minutes to an hour or more.

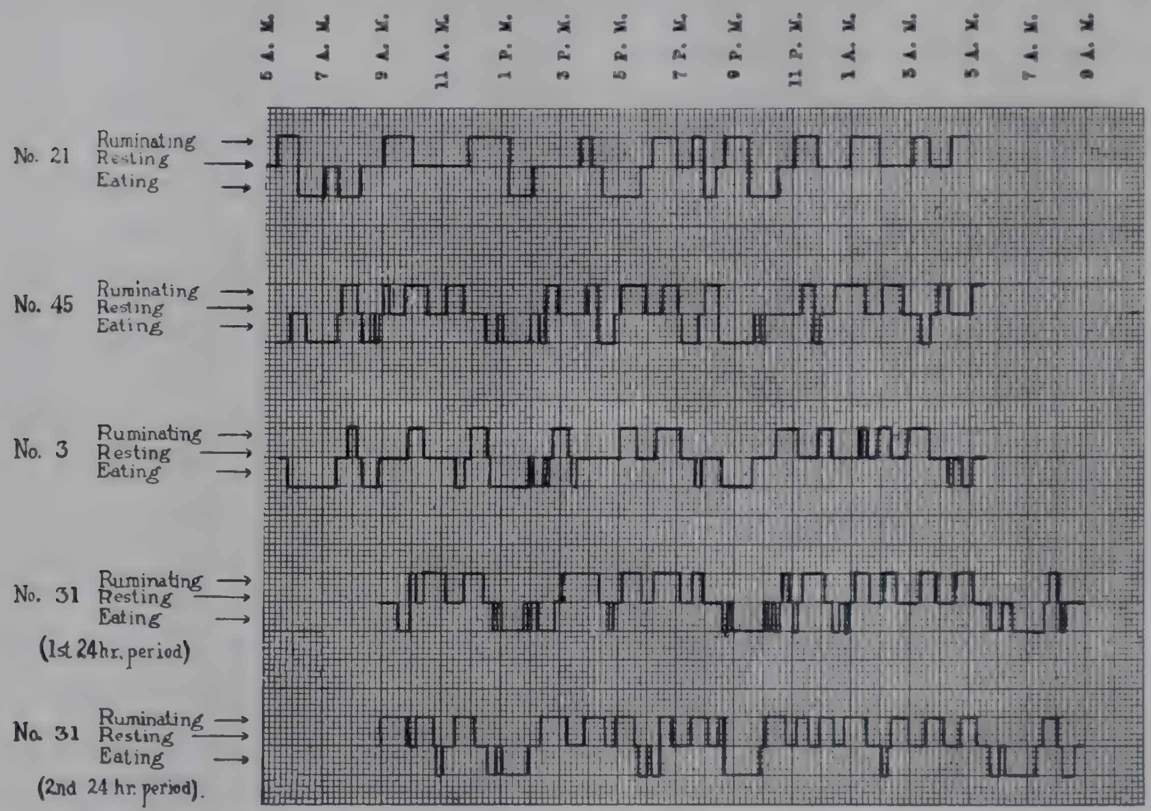


FIG. 90.—Showing the time spent by four cows in ruminating, resting, and eating, during a 24-hour period. (From Fuller, *New Hampshire Agricultural Experiment Station Bull.* 35, 1928.)

The average time devoted to a bolus (cycle of rumination) is somewhat less than one minute (cow). The average time required for regurgitation and redeglutition together is 3 or 4 seconds. The duration of the pause at the end of a cycle is 3 or 4 seconds.

The Nervous Control of Rumination. The act of rumination is undoubtedly reflex, although several of its phases can be influenced by voluntary control. The inspiratory effort responsible for the projection of food into the esophagus, the remastication, and the first stage of swallowing can be inhibited more or less completely; and if the ruminating animal is disturbed by external conditions, the act will usually be suspended or stopped altogether. Nevertheless, as it ordinarily occurs, rumination is quite reflex. The existence of a rumination center in the medulla oblongata is postulated. It is probable that such a center, if it exists, correlates the activity of a number of centers—respiratory, masticatory, deglutitory—concerned in rumination.

The efferent nerves of rumination are the motor and secretory nerves to the muscles (inspiratory, laryngeal, esophageal, masticatory, deglutitory, reticular) and glands (salivary, except mandibular) concerned. Rumination can occur, although with difficulty, even when the phrenics are cut, as an experiment by Flourens showed. Under such conditions the other inspiratory muscles produce the necessary negative pressure. The afferent nerve fibers of the rumination reflex are probably have receptors in the reticulum and the anterior part of the rumen and reach the brain via the vagi. It is probable that the desire to ruminate is related to augmented contractions of the reticulum and anterior part of the rumen induced by rough ingesta in the cardiac region. Traction on the floor of the reticulum and the ruminoreticular fold and squeezing the floor of the reticulum often cause the animal to ruminate. Section of the vagi is said to abolish rumination, probably by cutting the paths that mediate the desire to ruminate as well as by interfering with stomach motility.

Further information on the mechanical factors of digestion in the ruminant stomach may be obtained elsewhere (Scheunert; Mangold; Mangold and Klein; Stigler; Lenkeit). A comprehensive review covering all phases of the physiology of digestion in the ruminant is that of McAnally and Phillipson.

CHEMICAL AND OTHER FACTORS

Although it is known that important changes of a chemical nature take place in the ruminant stomach, exact knowledge of these is all too meager. However, recent years have seen the development of considerable research activity in this long-neglected field, and important observations of a quantitative nature have been made. It is now possible to speak in more definite terms regarding some of the chemical and related changes that go on in the ruminant stomach, and present evidence suggests that research interest in this field will continue at a level more commensurate with the importance of the problems to be solved. It is evident that the efforts of physiologist, biochemist, nutritionist, bacteriologist, and protozoologist are required.

For reviews of the physiology of digestion in ruminants, including the recent work, see McAnally and Phillipson, and Phillipson (1946). The significance of bacteria and protozoa in the rumen is reviewed by Hastings; see also the article by Gall. The papers by Quin (1943) and van der Wath and Myburgh contain important experimental findings and reviews of the literature.

Rumen and Reticulum. These compartments of the ruminant stomach are so closely related in all their physiological functions that they may well be considered together in the present discussion. In addition to their important motor functions, these compartments, especially the capacious rumen, serve as a place of extensive chemical and microbiological activities. The saliva of the ruminant contains no amylase and the rumen and reticulum add no secretion to their contents. However, it is known that a large number of microorganisms, both bacteria and protozoa, exist in the rumen and there is pretty general agreement that they are the main factors responsible for the digestion of carbohydrates there. Most workers believe that the microflora are of much more importance than the microfauna in the digestive processes. Other activities of the bacteria of the rumen are the synthesis of members of the vitamin B-complex (p. 527) and the conversion of nonprotein nitrogenous substances such as urea and ammonia into protein that can subsequently become available to the animal (p. 466).

Digestion of Carbohydrates. Plant enzymes may be of some importance in the digestion of carbohydrates in the rumen, but knowledge on this point is not impressive. Present evidence does not indicate that their role is large.

Bacteria are believed to be the main factors of carbohydrate digestion in the rumen. Two points of view have arisen regarding the manner in which bacteria produce products of nutritional importance to the animal. (1) The volatile fatty acids found in the rumen are the end-products of bacterial attack on food carbohydrates and when absorbed make an important contribution to the nutrition of the animal. (2) The bacteria convert cellulose and other food carbohydrates into products which they then build up into an intracellular polysaccharide; this is later hydrolyzed to glucose by enzymes present in the intestine.

It is considered that these views are not necessarily opposed to each other. It is possible that both may be correct—that the animal may absorb and make use of the lower fatty acids as such, and that it may also digest in the intestine and utilize a bacterial polysaccharide formed in the rumen. How much, if any, of the latter process goes on cannot be stated at present. That the former occurs as a normal process in ruminant digestion and nutrition has long been believed and may now be considered as established.

Elsden has studied the bacteria that are concerned in the production of the volatile fatty acids in the rumen and the effects of diet on the rumen flora. He emphasizes that further studies of the bacteria are required, "for it is certain that a vigorous microflora is one of the conditions essential for the health of the animal."

Cellulose is the main constituent of the crude fiber of vegetable foods. Herbivores in general and ruminants in particular digest and use large amounts of cellulose. It is now well established that important end-products of this digestion are a mixture of volatile fatty acids, especially acetic, propionic, and butyric. The steps in the formation of these substances from cellulose are not well understood. Glucose may be an intermediate substance. It is now known that the rumen can absorb. The suggestion seems reasonable that glucose, if formed in significant amounts in the rumen, may be absorbed directly as such. Probably some of the glucose is degraded through the stages of lactic acid or pyruvic acid to lower fatty acids.

Other polysaccharides including hemicelluloses and starch are fermented in the rumen. The products of their fermentation are thought to be similar to those formed from the fermentation of cellulose.

Volatile Acids of the Ingesta of Herbivores. Elsden and co-workers have investigated the volatile acid content of the ingesta found in different parts of the alimentary canal of sheep, ox, deer, horse, pig, rabbit, and rat. The regions of the alimentary canal in which fermentation occurs, as judged by the quantity of volatile acid present in the ingesta, are the rumen and reticulum in ruminants and the large intestine in all species. Acetic, propionic, and butyric acids make up over 85 per cent of the volatile acids of the rumen and large intestine. The relative proportions of these three acids are similar in all species studied (except the rat), the averages being acetic acid, 67; propionic acid, 19; butyric acid, 14. The amount of volatile acid present in the ingesta per kilogram of body weight was greatest in the ox and sheep. Calculations were made of the average amounts of volatile acids present in different parts of the alimentary canals of several animals. Some of the results are: rumen and reticulum of ox, 329 gm.; rumen and reticulum of sheep, 64 gm.; colon and cecum of horse, 236 gm. From the large intestine of a horse 342 gm. of volatile acid (expressed as acetic acid) were actually isolated.

Such results as these leave no doubt of the great importance of the volatile acids as end-products of carbohydrate digestion in ruminants and other herbivores.

Gases and Eructation. The gases of the rumen are principally carbon dioxide and methane. At times a considerable percentage of nitrogen may be present, but the actual amount of this gas in the rumen is usually not very great. Small amounts of oxygen, hydrogen, and hydrogen sulfide may also be present. The conditions in the rumen are essentially anaerobic. Carbon dioxide is produced by bacterial fermentation in the rumen. Probably a number of organic substances in the rumen can serve as sources of carbon dioxide. The former belief was that methane arose from cellulose fermentation, but it is now considered that it is formed by the reduction of carbon dioxide with the simultaneous oxidation of substances such as alcohols or lower fatty acids.

Saliva contains a great deal of carbon dioxide in the form of carbonates. When the reaction of the rumen ingesta is acid, saliva in the rumen may serve as a source of carbon dioxide (Cole and co-workers).

The composition of rumen gases is little influenced by the kind of ration eaten, but it varies greatly with the time elapsing after feeding (Fig. 91). Likewise the total amount of gas formed bears little relation to the kind of ration, but it rises sharply after eating and then falls gradually (Fig. 92). The amount of food eaten and the amount of gas formed are directly related (Cole, Mead, and Kleiber).

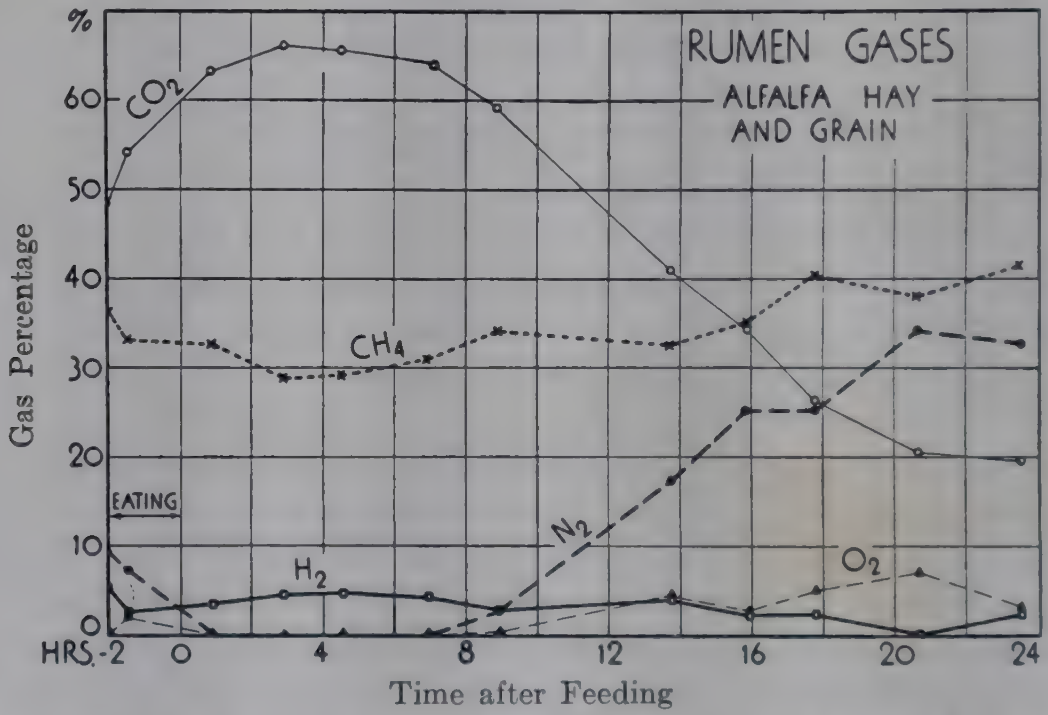


FIG. 91.—The composition of rumen gases (dairy cow) on a ration of alfalfa hay and grain. (From Washburn and Brody, *Missouri Agricultural Experiment Station Research Bull.* 263, 1937.)

The gases of the rumen may be expelled by eructation, or belching, and by absorption into the blood. Most of the gas so absorbed would be eliminated through the lungs. It is possible that some of the carbon dioxide of the rumen is removed by bacteria, which use it in their metabolic processes.

Eructation occurs at the height of a rumen contraction, but every rumen contraction is not accompanied by belching. When the intraruminal pressure is experimentally increased by forcing gas into the rumen, belching still occurs only during rumen contraction, even though the intraruminal pressure between contractions is higher than the pressure normally present during belching. It is held, therefore, that some factor in addition to pressure must be concerned in eructation. It appears that reflex relaxation of the cardia is also necessary, the stimulus for the reflex being provided by the scratching of roughage on the rumen mucosa (Cole, Mead, and Kleiber).

Bloat. This is the overdistention of the rumen with gas. It is a serious practical problem in cattle and sheep husbandry. Bloat may be divided into acute and chronic types. Acute bloat is the kind that is related to feeding practices and is the one considered here. As noted above, neither the total amount nor the composition of the rumen gas is much influenced by the kind of feed. However, the composition and the amount formed change markedly after feeding. There is a direct relationship between the total amount of gas formed and the amount of food eaten. Recent studies show that these generalizations also apply in bloat. It is not the composition of the rumen gas that has changed, nor is the amount produced in bloat significantly increased.

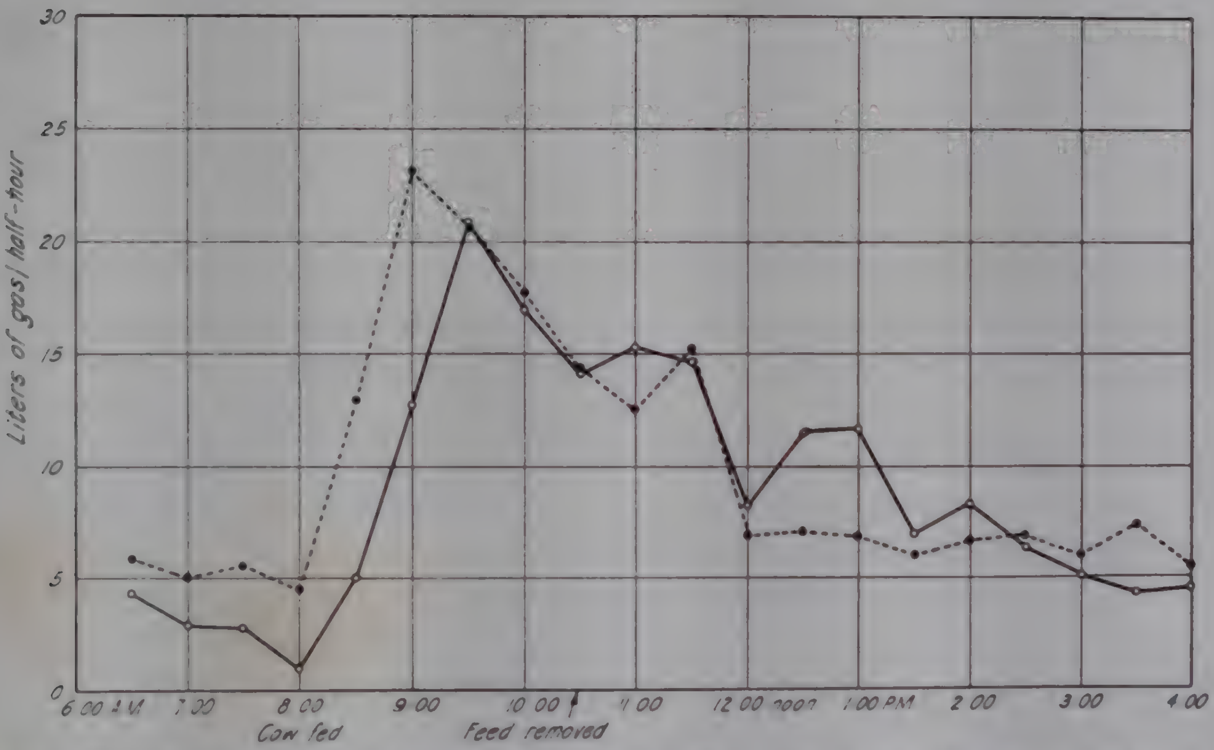


FIG. 92.—The rate of gas formation in a cow after eating. The broken line shows the average of three tests on a full feed of alfalfa hay; the solid line, the average of five tests on a full feed of green alfalfa. The rate of gas formation is shown in liters per half-hour. Note the general similarity of the two curves. (From Cole, Mead, and Kleiber, *California Agricultural Experiment Station Bull.* 662, 1942.)

Acute bloat is most commonly seen in animals pastured on thick immature stands of alfalfa or clover. Bloat is usually not a serious problem when animals are pastured on grasses. Modern work indicates the the main problem in bloat hinges around the expulsion of gas rather than its production. Roughage in the diet stimulates the eructation reflex and gas is expelled. In acute bloat, at least in some important forms of acute bloat, there is not enough roughage in the ration to stimulate the belching reflex and gas accumulates in the rumen and reticulum. This form of bloat is successfully prevented by getting more roughage into the diet to stimulate the eructation reflex.

The rumen wall is normally permeable to gas. It is possible that in bloat a decreased permeability of the rumen wall to gas, or a diminished capillary circulation because of increased intraruminal pressure, may be a factor. However, the evidence on these points is meager.

In so-called frothy bloat there is foaming of the rumen ingesta and the gas is not readily expelled by eructation or through a cannula inserted in the rumen. Some observers consider this to be a common form of bloat, different from simple bloat in which rumen gas is largely free from the mass of ingesta. It is held that saponin in certain plant foods may be responsible for the foaming (Quin, 1943).

The cause of death in bloat is unknown. Apparently the rise of pressure in the rumen of bloated animals is not great enough by itself to account for death. The absorption of toxic substances (hydrogen sulfide, carbon monoxide, histamine, etc.) may be a factor.

The results of recent work on bloat may be found in a bulletin by Cole, Mead, and Kleiber and in a review by Cole and co-workers. The latter publication contains an extensive bibliography on bloat.

Reaction of Ingesta. A number of recent studies have been made (Hale, Duncan, and Huffman; Monroe and Perkins; Olson, 1941; Villares; Wegner and co-workers; Smith, 1941; Phillipson, 1942). Most of the results indicate that the reaction of rumen contents is just on the acid side of neutrality. Most of the values fall in the range of *p*H 6.0 to 7.6. The changes of *p*H are a manifestation of the changes in the amounts of organic acids that are present in the rumen as a result of the fermentation of ingesta there. The rate and magnitude of the changes in *p*H depend on the diet and on the rate of absorption from the rumen. Variations observed during the day and with different rations are shown in Fig. 93.

Omasum. The material in the omasum is much drier than that in the rumen or the reticulum, its water content being only from 50 to 65 per cent. Such a condition of low moisture is not favorable to the operation of the chemical factors of digestion. The average reaction of the omasal contents of the ox is *p*H 7.2 (Schwartz and Stremnitzer) and is therefore just on the alkaline side of neutrality.

Abomasum. This, the glandular portion of the ruminant stomach, presents fundic and pyloric zones with their respective kinds of glands.

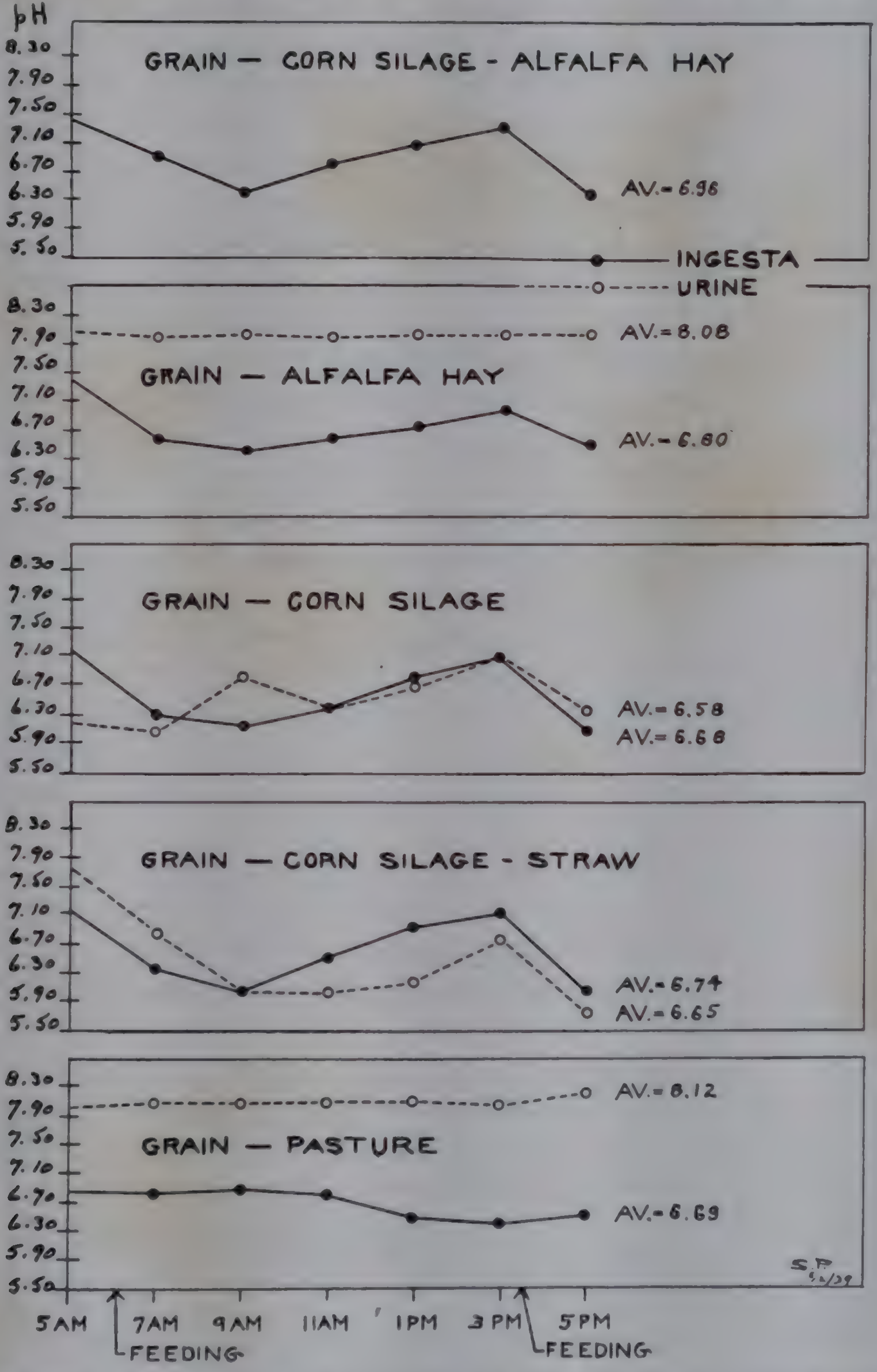


FIG. 93.—The pH of samples of rumen ingesta obtained from a cow by means of a rumen fistula. The effects of various rations are shown. Evidently the changes in pH attributable to the differences in the rations used were small. The pH of the urine is also shown. (From Monroe and Perkins, *Journal of Dairy Science*, 1939, **22**.)

Their secretion is gastric juice; so the function of the abomasum is essentially the same as that of the simple stomach. The water content of abomasal ingesta is high—80 to 90 per cent. The concentration of volatile acids in the ingesta is low.

Pure gastric juice has been obtained from the goat (Bickel, Grosser) and calf (Belgowski; Shoptaw, Espe, and Cannon; Espe and Cannon, 1937) and has been found to be similar in composition and action to that of simple-stomached animals. The concentration of hydrochloric acid is somewhat less than in the gastric juice of man and carnivores. The hydrogen ion concentration of the abomasal contents of cattle varies from *p*H 2 to 4.1 (Schwarz and Kaplan). The freezing point of abomasal contents of sheep is practically the same as that of blood; the range is —0.555 to —0.610 degrees C. (Davey).

The effect of heat treatment of milk on the abomasal emptying time and abomasal acidity of calves has been studied (Mortenson, Espe, and Cannon). Heat-treated milk leaves the abomasum more quickly than raw milk. Apparently variations in the acidity of the gastric juice when the heated and raw milks were fed were not great enough to account for the differences in evaluation time. The lowering of the curd tension by the heat was probably an important factor in the quicker evacuation time when heated milk was fed.

The effect of various foods (whole milk, skim milk, soybean gruel) on the rate of secretion of gastric juice and on the free and total acidity of the abomasal contents has been studied in calves (Shoptaw, Espe, and Cannon).

Psychic secretion of gastric juice is slight or absent in ruminants. This has been determined on calves with Pavlov pouches (Espe and Cannon, 1937). A calf teased with food or a calf with an esophageal fistula subjected to sham-feeding (Fig. 94) shows no significant increase in the secretion of gastric juice.

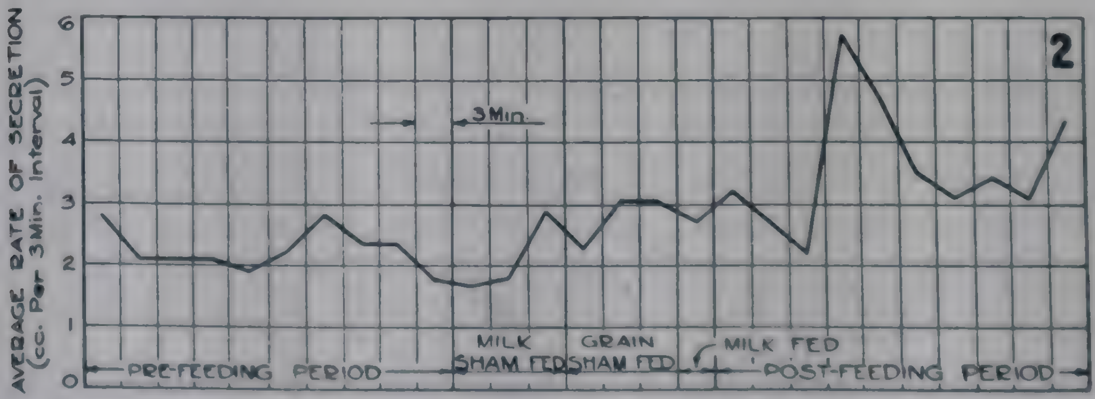


FIG. 94.—Effect of sham-feeding on the secretion of gastric juice by a calf. Esophageal fistula and Pavlov pouch (abomasum). (From Espe and Cannon, *American Journal of Physiology*, 1937, 119.)

ABSORPTION FROM THE RUMINANT STOMACH

Until recently it was generally believed that absorption from the ruminant stomach does not occur. The epithelium, particularly in the first three compartments, was held to be structurally unfavorable to absorption. The epithelium of the rumen has recently been studied histologically and compared with the epithelium of the skin (Barcroft, McAnally, and Phillipson, 1944a). It is evident from this study that rumen epithelium is more favorable to absorption than is skin epithelium. The capillaries of the rumen mucosa come into intimate relation with the deep epithelial cells. The omasal epithelium is similiar to that of the rumen, and the leaves are well supplied with blood.

Recent experiments require extensive revision of our ideas on absorption from the ruminant stomach. Working with sheep and goats, Trautmann made fistulous openings into the different stomach compartments; through these openings aqueous solutions of drugs of known physiological action (pilocarpine, atropine) were introduced. Care was taken to localize the drug solution in the place where it was introduced. Following the use of pilocarpine, licking, chewing, salivation, swallowing, and other symptoms of the systemic action of the drug were noted. The introduction of atropine caused the effects of pilocarpine to disappear. Evidence of absorption was obtained from all four compartments, but the first three absorbed more rapidly than the abomasum.

Rankin made observations on the absorption of glucose, potassium iodide, pilocarpine, strychnine, and sodium cyanide from the rumen of sheep. Care was taken to insure localization in the rumen of the substances tested. In all cases evidence of absorption was obtained. Glucose in the concentration introduced into the rumen caused an unmistakable rise in the blood sugar level. The glucose solutions used were strong. Further experiments are desirable in which glucose in weaker concentration is used. The drugs caused systemic effects.

Barcroft, McAnally, and Phillipson (1944b) demonstrated that absorption of lower fatty acids occurs from the rumen of the sheep. The concentration of the acids in the blood obtained from veins that drain the rumen was determined and found to be definitely higher than that in peripheral blood. It was shown in a similar way that absorption of volatile acids occurs from the reticulum, omasum, and cecum but not from the abomasum and small intestine. The amount absorbed from the omasum was less than from the rumen. The results clearly show that lower fatty acids in nutritionally significant amounts are absorbed from the alimentary canal of the ruminant.

Danielli and co-workers have continued the work on absorption from the ruminant stomach begun by Barcroft and co-workers. A study was made of the mechanism of absorption from the rumen as it affects the lower fatty acids, acetic, propionic, and butyric. Absorption of the lower fatty acids from the rumen is influenced by the *p*H of the rumen contents. At lower *p*H values, for example, 5.8, more absorption occurs than at higher values, for example, 7.5. This is due to the fact that at the lower *p*H values free fatty acid as well as the fatty acid anion is absorbed, whereas at alkaline *p*H only the fatty acid anion is absorbed, free fatty acid being present only in negligible amounts. However, absorption of volatile fatty acids (in whatever form) in considerable quantity occurs at all *p*H values ordinarily found in the rumen. The studies involved considerations of the permeability of the rumen epithelium. It was concluded that the fatty acid anion is absorbed through water-filled pores, which probably lie in the intercellular cement substance of the rumen epithelium. The free fatty acid is absorbed in part through water-filled pores but to a greater degree through the epithelial cells themselves. It was also concluded that the permeability of the rumen epithelium to free acid in the rumen ingesta is an important factor in the control of rumen *p*H, insuring a tendency toward neutrality in addition to, and independently of, the buffering action of saliva.

Chapter XV

DIGESTION IN THE SMALL INTESTINE

THE material leaving the stomach and entering the intestine is known as chyme. Its consistency is fluid or semifluid and its reaction is acid. It is composed of water, hydrochloric acid, inorganic salts in great variety, and many kinds of organic substances such as acid metaprotein, proteoses, peptone, starch, dextrins, and maltose (in animals possessing salivary amylase), gums, cellulose and related compounds, liquefied fats, and many other substances, depending upon the diet and feeding habits of the animal. The water content of ingesta in the small intestine is high, varying from 60 to 95 per cent in different species.

In the intestine the chyme undergoes important changes, which constitute intestinal digestion. In the small intestine the factors of digestion are pancreatic juice, bile, intestinal juice, and certain movements of the intestinal wall. The movements will be discussed in the next chapter.

PANCREATIC JUICE

The pancreas closely resembles in structure the parotid salivary gland. It is a compound tubulo-alveolar gland pouring its secretion into the duodenum by means of the pancreatic duct. In the horse and dog there are usually two ducts. The arrangement of the duct system in mammals is discussed by Huntington. The secreting alveoli are grouped into lobules and these into lobes. Throughout the pancreas is found a connective tissue framework giving support to the alveoli, lobules, and lobes. Lying in the connective tissue between the alveoli are collections of polyhedral cells known as the pancreatic islet or islands of Langerhans. These structures, different from the groups of cells (alveoli) concerned in the production of pancreatic juice, produce an internal secretion that plays an important part in carbohydrate metabolism. The pancreas may therefore be regarded physiologically as two organs in one. The alveoli produce the digestive juice. The islets produce the internal secretion insulin. The β-cells of the islets are believed to be the source of insulin. The present problem deals with the external secretion, pancreatic juice. Insulin will be studied in another chapter. For the significance of lipocaic, see p. 476.

Composition and Amount. Samples of pancreatic juice may be obtained from a cannula inserted into the pancreatic duct or from a permanent fistula of the duct. Pancreatic juice is a clear, distinctly alkaline liquid which coagulates on heating. The *p*H of the juice obtained from permanent fistulas in dogs ranges from 7.16 to 8.04 (Johnston and Ball). The percentage composition of the juice from a permanent fistula in the dog is as follows (C. Schmidt, cited by Vierordt):

Water	98.04
Solid matter	1.95
Organic matter	1.27
Ash	0.68
Specific gravity	1.01

The amount of pancreatic juice secreted per kilogram of body weight per day in the domestic animals is, according to the old work of Colin (cited by Vierordt), as follows: horse, 16.8; ox, 14.4; sheep, 12.0; pig, 7.2; dog, 2.4 gm. From these figures it may be calculated that the daily amount of pancreatic secretion in a 455-kg. (1000-pound) horse is more than 7 liters; in a 455-kg. ox, more than 6 liters, etc. In man it is estimated that the daily amount is 700 to 1000 cc.

Action. Pancreatic juice shows the presence of several proteolytic enzymes, a lipolytic, and an amylolytic enzyme.

Proteolytic Enzymes. At least three proteolytic enzymes occur in pancreatic juice: trypsinogen, chymotrypsinogen, and carboxypeptidase. *Trypsinogen,* present in the pancreatic juice obtained directly from the pancreatic duct, is activated by the enzyme *enterokinase,* found in the intestine. The activated substance is termed *trypsin.* This enzyme converts proteins and partly hydrolyzed proteins into peptides and amino acids. Trypsin appears to be present in all animals. The optimum *p*H for its action is about 8. Trypsin has been prepared in crystalline form. *Chymotrypsinogen* is changed to *chymotrypsin* by the action of trypsin in the intestine. It converts proteins and partly hydrolyzed proteins into peptides and amino acids. Chymotrypsin shows a powerful coagulating action on milk. It has been prepared in crystalline form. *Carboxypeptidase* acts on peptides containing a free carboxyl group and splits off an end amino acid. Carboxypeptidase has been prepared in crystalline form.

Pancreatic Lipase (Steapsin). This enzyme has the power of hydrolyzing fats to fatty acids and glycerol. As has already been stated, the amount of fat digestion in the stomach is slight. Liquefied fat upon entering the intestine encounters alkaline juices in the upper part of the intestine, whereupon any free fatty acid in the fat is converted to soap. This, aided by the churning action of the intestinal movements, emulsifies the neutral fat. Emulsification hastens fat hydrolysis because of the large fat surface presented for enzymic action. The fatty acids released by hydrolysis are themselves insoluble in the medium present in the intestine. They combine with bile salts to form water-soluble, diffusible compounds. Not only are the bile salts of value in holding in solution otherwise insoluble fatty acids but they have an activating effect on lipase. Their action in this respect is believed to be nonspecific (Waldschmidt-Leitz).

In the form of fatty acids and glycerol, therefore, fats are absorbed. However, the possibility is not excluded that some fat is absorbed in unhydrolyzed form, perhaps in a state of molecular fineness (p. 387).

Lecithinase, an enzyme capable of hydrolyzing the phospholipid lecithin, is said to be found wherever lipase is found.

Pancreatic Amylase (Amylopsin). This enzyme is present in the pancreas and the pancreatic juice of all vertebrates. It resembles salivary amylase in many respects and hydrolyzes starch and the various dextrins to maltose. Some observers claim that amylopsin consists of more than one enzyme: an amylase proper, which hydrolyzes starch to dextrin, and one or more dextrinases, which hydrolyze dextrins to maltose. According to Groll, the optimum hydrogen ion concentration for the action of amylase from fresh pig pancreas is pH 5.5 to 6; from ox pancreas, pH 6.7; from human pancreatic juice, pH 7.4. Bile probably has a slight accelerating influence on the amylolytic action of pancreatic juice. Certain ions, particularly Cl, are necessary for the action of pancreatic amylase.

Other Enzymes. Sucrase (invertase) and maltase, enzymes that hydrolyze surcose and maltose, respectively, into their constituent monosaccharides, have been found in the pancreas; but the amount present is not large. These enzymes and lactase are found more abundantly in the small intestine.

Digestive Importance of Pancreatic Juice. In spite of the importance of pancreatic juice in the digestive processes, it is not indispensable, at least in dogs (Coffey, Mann, and Bollman, 1940c). Various procedures—complete pancreatectomy, complete pancreatic fistula, evulsion of the pancreatic ducts—can be used to prevent the entrance of pancreatic juice into the intestine. Following the complete absence of pancreatic secretion, large amounts of fat and carbohydrate appear in the feces. Protein digestion and absorption are little affected, although nitrogen excretion in the feces is increased. A small amount of pancreas suffices to carry on the digestive work of the pancreas.

THE REGULATION OF PANCREATIC SECRETION

Nervous Control. The control of the secretion of pancreatic juice was for many years a very live research topic in physiology. Pavlov and his associates showed that secretory nerve fibers reach the pancreas principally by the vagi and, to a lesser extent, by the splanchnic nerves. When the peripheral end of the vagus is stimulated the blood pressure falls. To prevent this undesirable side effect the vagus nerve may be transected several days before it is to be stimulated. During this time the cardio-inhibitory fibers lose their irritability, whereas the secretory fibers of the pancreas remain unaffected. Stimulation of the peripheral end of the vagus now causes secretion. The cardiac effect may be prevented by stimulating the vagus nerve in the thorax below the origin of the cardiac branches. That nerve impulses are normally concerned in the secretion of pancreatic juice is further shown by the observation (Pavlov, Ivy) that a dog with a pancreatic fistula secretes pancreatic juice when sham-fed. This indicates that nervous influences that develop as a result of the sensations of eating are at work. It may therefore be concluded that pancreatic secretion, like gastric secretion, shows a preliminary stage in which cephalic nervous stimuli are effective. The amount of juice secreted during the cephalic phase is small.

Hormonal Control: Secretin. Pavlov and his pupils also showed that when acid is introduced into the duodenum the pancreas secretes. Since this effect takes place even when the vagi are cut, they held it to be of the nature of a peripheral reflex through the ganglia of the pancreas, most of which are situated close to the duodenum.

Bayliss and Starling (1902) reinvestigated the question of the acid stimulus of pancreatic secretion and found that secretion takes place even when acid is introduced into a loop of denervated jejunum. Since acid introduced directly into the blood stream has no effect, these investigators suspected that some substance is formed in the wall of the intestine by the action of acid and is then transported by the blood to the pancreas where it exerts its stimulating effect. They therefore extracted the scrapings from the mucous membrane of the jejunum with hydrochloric acid, filtered and neutralized the extract, and injected it into a vein. The result was that the pancreas secreted copiously. To the substance extracted from the lining of the intestine and activated by hydrochloric acid, Bayliss and Starling gave the name *secretin*. They showed that it is a thermostable substance. To chemical excitants formed in the body and transported in the blood stream they gave the general name hormone.

The chemical or humoral control of the pancreas has been studied by Ivy and Farrell (1926) and Ivy, Farrell, and Lueth. It was shown that a piece of pancreas permanently transplanted under the skin would secrete after the animal was fed. This proved that an excitant was carried to the transplant via the blood stream. Later, indubitable evidence was brought forward that the humoral agent in question is a hormone. A Thiry-Vella fistula was made from the jejunum of a dog, the tail of whose pancreas had been previously transplanted under the skin. In another dog a loop of jejunum was transplanted under the skin and a pancreatic transplant was made. In either case when a weak solution of hydrochloric acid—a pure chemical substance which when introduced parenterally does not cause the pancreas to secrete—was applied to the loop, the pancreas would begin to secrete in a short time. These experiments afford convincing proof that something (a hormone) was formed in the loop as a result of the acid application and was carried by the blood to the pancreatic transplant, which it then stimulated to secrete. The investigators believe that the mechanism operates in the normal individual.

Hydrochloric acid is not the only substance which upon entering the intestine arouses the pancreas to secrete. Fats, fatty acids, soaps, meat, starch, water, and other agents are effective.

Necheles and Lim have made a contribution to our knowledge of the hormone for pancreatic secretion. They submitted the circulating blood of dogs to dialysis (vividialysis) and injected the dialyzate into the blood stream of other dogs, whereupon the pancreas of the injected dogs secreted. It was further found that the pancreatic excitant could be increased in amount in the dialyzed blood by feeding or by the injection of hydrochloric acid into the duodenum. This is strong evidence that the mechanism is normal.

Bayliss and Starling (1902) held that secretin exists in the epithelial cells of the small intestine in the inactive state, prosecretin, which upon coming in contact with hydrochloric acid from the stomach is converted into active secretin. This is then absorbed into the portal blood and carried to the pancreas, where it exerts its action. Work by Mellanby led him to the conclusion that secretin probably exists in the wall of the intestine in an active form; but the matter is not fully settled. Secretin has been prepared in crystalline form. It is probably a peptide.

The distribution of secretin varies considerably in different species (Mellanby). In the cat it is found practically only in the duodenum. In the pig considerable amounts occur at least 10 feet from the pylorus. In the goat it is found not only in the duodenum but also in the ileum. In the dog Weaver found secretin occurring principally in the duodenum. It has been found in the small intestine of the fetus.

It has long been known that pancreatic juice formed under the action of secretin is copious in amount, poor in protein and enzymes, and rich in sodium bicarbonate, whereas that produced under vagal stimulation is scanty in amount but rich in protein and enzymes.

Secretin appears to act directly on the secretory cells of the pancreas and not on the nerve terminations. It is without effect on the gastric glands but it stimulates the secretion of bile.

Hormonal Control: Pancreozymin. Recently a substance has been extracted from the mucosa of the small intestine of the pig, dog, and cat which when injected into cats causes an increased secretion of enzymes by the pancreas but is without effect on the volume of juice formed (Harper and Raper). The substance has been designated as *pancreozymin*. It is thermostable. It has a distribution in the small intestine similiar to that of secretin. Pancreozymin is effective on the pancreas after vagus transection or the injection of atropine. It is distinct from secretin and cholecystohinin (p. 353). It appears to be a hormone which, like the vagi, regulates the secretion of enzymes by the pancreas. Secretin controls the volume and bicarbonate content of the juice.

INTESTINAL JUICE

The Glands of the Intestine. The intestine of all animals shows the presence of two kinds of glands, intestinal and duodenal. The intestinal glands (crypts of Lieberkühn) are simple tubular glands found throughout the small and large intestine. They are limited to the mucous membrane, that is, they do not extend into the submucosa. They show the presence of many goblet cells. The secretion of these glands is known as intestinal juice or succus entericus.

The duodenal (Brunner's) glands do not occur throughout the intestine; they are limited to the first part of the small intestine. In all animals they begin at the pylorus, but their backward extent varies greatly in different species. The duodenal glands are tubulo-alveolar in type; and the secreting portion is found principally in the submucosa, although it may occur in the deeper parts of the mucous membrane. The ducts of the duodenal glands generally open on the surface of the mucous membrane between the villi, though in some instances into the fundus of the intestinal glands. Considerable interspecific structural differences in the duodenal glands of domestic animals have been recorded (Elias, 1947b). The secretion of the duodenal glands is known as duodenal juice. Numerous glands in the submucosa of the ileum of the ox have been reported (Elias, 1947a). Their significance is unknown.

Methods of Obtaining Intestinal Juice and Intestinal Contents. Intestinal juice proper, that is, the secretion of the intestinal glands, may be obtained in pure form by means of a Thiry fistula or a Thiry-Vella fistula. In either operation a segment of intestine is isolated except for its mesenteric attachment, and the continuity of the bowel is re-established. In Thiry's method one end of the excised loop is closed and the other end is brought to the surface of the body by being fixed into an opening in the abdominal wall. Vella's modification consists in fixing both ends of the isolated loop into openings to the outside (Fig. 95). From the opening or openings intestinal juice can be obtained. The fistula as usually made (dog) is below the duodenal gland zone, so that the secretion represents intestinal juice proper. Simple fistulas into the lumen of the intestine obviously do not yield pure intestinal juice.

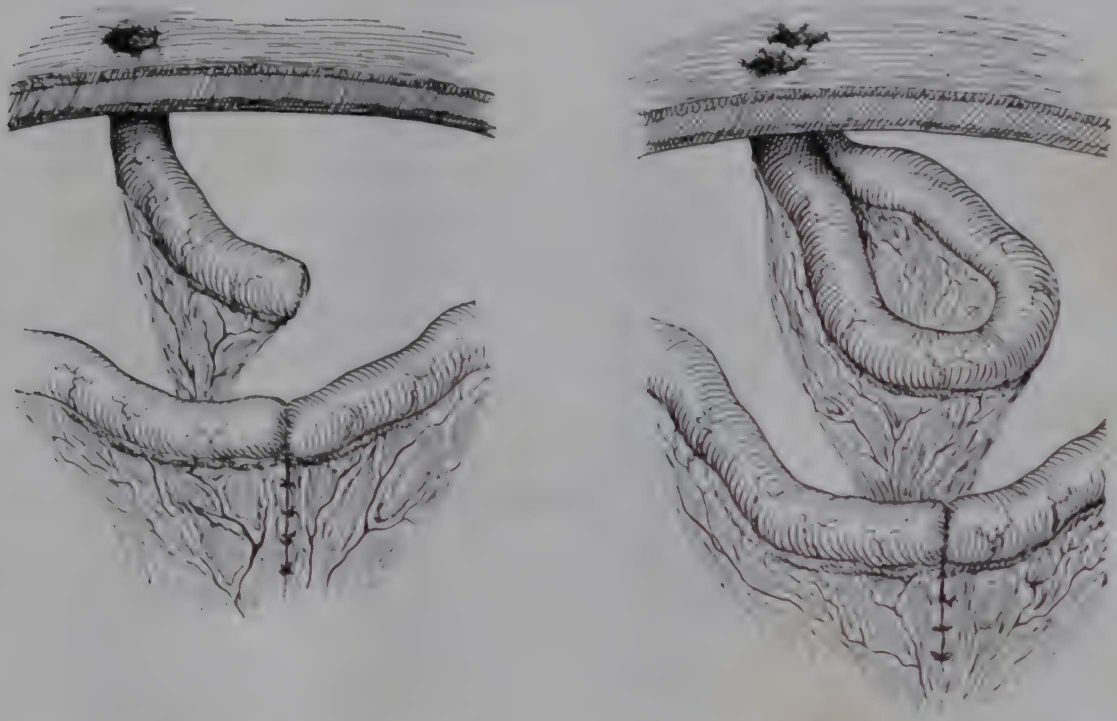


Fig. 95.—Diagram of Thiry fistula (left) and Thiry-Vella fistula (right). (From Markowitz' *Textbook of Experimental Surgery,* William Wood and Company, 1937.)

Up to the present time it has been found impossible to obtain duodenal juice in pure form. This is because of the intimate anatomical relation of the duodenal glands to the intestinal glands.

Intestinal contents may be obtained for study by means of a simple fistula of the bowel or, better, by means of the Mann-Bollman fistula. This fistula can be made at any level of the gastro-intestinal tract. A Mann-Bollman fistula of the terminal portion of the ileum is shown in Fig. 96.

Composition. Many investigators have obtained pure intestinal juice from the dog by means of a Thiry fistula or some modification of it. From a lamb (Pregl), a goat (Lehmann), and pigs (Lohscheidt) intestinal juice has been obtained by means of fistulas. Intestinal juice is described as a colorless or pale-yellow, usually somewhat turbid liquid of alkaline or slightly acid reaction and a specific gravity of about 1.01. According to Thiry (cited by Vierordt) the percentage composition of the juice of the dog is as follows:

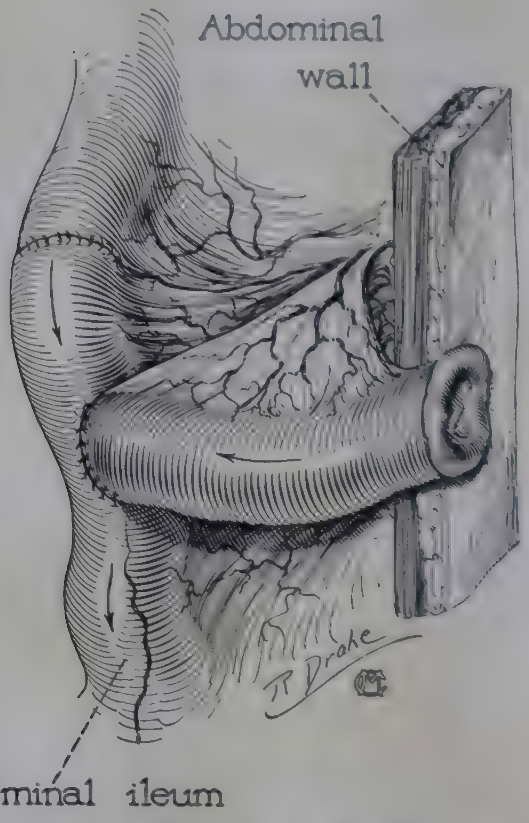


FIG. 96.—Fistula of the terminal portion of the ileum. A piece of intestine is resected and used as a fistulous tract to the bowel. The piece is so directed that its peristaltic activity will prevent leaking. This type of fistula can be made at any level of the gastro-intestinal tract. (From Mann and Bollman, *Annals of Surgery*, 1931.)

Water	97.59
Protein	0.80
Other organic substances	0.73
Inorganic salts	0.88

Modern studies are in close agreement with these results. From isolated jejunal loops with intact blood, lymph, and nerve supplies, de Beer, Johnston, and Wilson obtained a juice whose average composition was as follows: water, 97.46 per cent; solids, 1.66 per cent; ash, 0.88 per cent; *p*H 6.8.

Pregl found that the juice obtained from a fistula situated well down the intestine of a lamb contained nearly 3 per cent of solids, including sodium bicarbonate, protein, urea, and other substances. Its specific gravity was 1.014.

It is difficult to get an accurate idea of the amount of juice secreted by the entire intestine in a given time. Pregl estimated that the whole intestine of a lamb secretes nearly 3 liters in 24 hours. Estimates in man range from 700 to 3000 cc.

Action. The question of the digestive action of intestinal juice resolves itself into one of the enzymic properties of the juice. A number of enzymes have been described in intestinal juice and in extracts of intestinal mucous membrane. Some investigators report that enzymic action of extracts of the mucous membrane is much greater than that of the juice itself. This leads to the belief that the enzymes under consideration are chiefly endo-enzymes, exerting their action on the foods during absorption. Such a view receives further support from the fact that most intestinal enzymes act on intermediary products of digestion—products which from the physicochemical point of view should be absorbable but which for physiological reasons must undergo further hydrolysis, as they pass through the wall of the intestine. Modern work on the enzyme activity of intestinal juice has been done by Cajori, who found that peptone, sucrose, and lactose are absorbed more rapidly from intestinal loops than could be accounted for on the basis of enzyme activity of the juice. It appears therefore that endo-enzymes exist in the wall of the intestine. The subject is discussed in a review on the secretions of the intestine by Florey, Wright, and Jennings.

The following enzymes have been described in intestinal juice or in extracts obtained from the intestinal mucosa.

Enterokinase. This enzyme activates trypsinogen, the proteolytic enzyme of the pancreas (p. 336).

Peptidases. Several peptidases (old name, erepsin) are present in the mucous membrane and the juice of the intestine. Peptidases convert peptides to amino acids.

Maltase. This enzyme converts maltose into glucose. It is present also, in small amounts, in human saliva and in pancreatic juice.

Sucrase (Invertase, Saccharase). This disaccharidase hydrolyzes sucrose to glucose and fructose.

Lactase. This enzyme splits lactose into glucose and galactose. It is present in the intestine of all young mammals but may be lacking in mature mammals that do not receive milk in their food.

Lipase. This enzyme, which is similar to pancreatic lipase, undoubtedly occurs in the intestine.

Amylase. An amylolytic enzyme is found in significant amounts in intestinal juice (Cajori). Extracts of intestinal mucosa also contain an amylase, but it may be of blood origin.

Polynucleotidase, Nucleotidase, and Nucleosidase. Nucleoproteins are widely present in foods of both plant and animal origin. They are conjugated proteins composed of a protein fraction and nucleic acid. Under the influence of gastric and pancreatic digestion, nucleoproteins are split into protein and nucleic acid. The protein is digested in the usual manner; the nucleic acid is digested by enzymes of the intestinal juice and mucosa.

Nucleic acids are made up of four radicals known as nucleotides. They are therefore sometimes designated as tetranucleotides. A nucleotide is a combination of phosphoric acid, pentose, and purine or pyrimidine base. When the phosphoric acid is split off from a nucleotide, a nucleoside is left. It is a pentose-base combination.

Polynucleotidase is an enzyme which splits nucleic acid into its constituent nucleotides. Another enzyme—nucleotidase, a phosphatase—hydrolyzes nucleotides to nucleosides and phosphoric acid. As indicated above, nucleosides are combinations of pentose and a purine or pyrimidine base. The purine nucleosides are hydrolyzed to purine bases and pentose by the action of a third enzyme, nucleosidase. Further action on the pyrimidine nucleosides apparently does not take place. In the form therefore pyrimidine nucleosides, phosphoric acid, purine bases, and pentose, nucleic acids are believed to be absorbed.

The Regulation of Intestinal Secretion. The regulation of the secretion of intestinal juice has not been as extensively studied as has the regulation of gastric and pancreatic secretions. It is generally recognized that mechanical stimulation of the intestinal mucosa causes secretion of intestinal juice. The importance of the extrinsic nerves in the control of the secretion has long been a question. Recent experiments by Wright and co-workers show that the nerves play a part, but it is not yet clear what their functions are. Stimulation of the vagi causes secretion, principally from the duodenal gland area. The sympathetic nerves apparently inhibit secretion, for transecting them causes secretion from all of the small intestine. That a humoral mechanism is involved in stimulating the glands seemed probable from the work of several investigators (Ivy, 1930) and appears to be proved by the recent experiments of Nasset, Pierce, and Murlin. In this work loops of jejunum (dog) were transplanted to the submammary tissue. After a time the original circulation and innervation of the loops were abolished by severing the mesenteric pedicle of the loops. Food in the digestive tract was accompanied by an increased rate of secretion from the isolated loops, as well as by an increased production of enzymes. Thus it is evident that both the rate of secretion and the production of enzymes of the intestinal glands are under humoral control. Later work indicates that the excitant is a hormone. *Enterocrinin* is the name given to the hormone. It has been obtained from the small and large intestines of several species (Nasset). Enterocrinin is believed to act by exciting the intestinal gland cells directly.

The Duodenal Glands. As previously stated, the secretion of the duodenal glands has never been obtained in pure form. Therefore their exact function is unknown. Bergman, Dukes, and Yarborough found that extracts of the submucosa in the duodenal gland zone of all domestic animals showed the presence of an amylase. However, they were unable to determine whether the enzyme was produced by the glands or merely owed its presence to tissue fluid in the gland substance. Yet, owing to the marked amylolytic action of duodenal gland extracts when compared with the action of extracts obtained from other parts of the intestine and elsewhere, they were led to believe that the glands themselves produce an amylase. No lipase or protease was found. Pavlov expressed the belief that the duodenal glands produce an amylase, and this view is held by several other workers.

Florey and Harding (1934, 1935a) have made an extensive study of the secretion of the duodenal glands, or more precisely the secretion of the upper part of the duodenum, in a number of species. Segments of the upper part of the duodenum were cut out and made into fistulas, one end of the loop being closed and the other communicating with the outside through an opening in the wall of the abdomen. The bile and pancreatic ducts were not disturbed. Successful fistulas were made in the goat, pig, dog, cat, and rabbit. Only partial success was attained in sheep. The duodenal juice in all species examined was viscous and sticky. This is due to the presence of mucins or pseudomucins. The specific gravity was practically the same in all species: goat, 1.007-1.008; pig, 1.007; cat, dog, and rabbit, 1.009. The amount of organic solids was about 0.5 per cent in all cases. The juice from all animals studied was distinctly alkaline: goat, *p*H 8.2-8.4; pig, *p*H 8.4-8.9; cat, *p*H 8.7-8.9; dog, *p*H 8.4; rabbit, *p*H 8.6-8-9; sheep, *p*H 8.3-8.4. The bicarbonate content varied widely. The juice from the goat and sheep showed little bicarbonate, while that from the rabbit contained a considerable amount. Other species occupied an intermediate position.

The amount of the secretion was large. Under comparable conditions the amount secreted in a particular animal was remarkably constant. In a goat a fistula about 5 cm. long secreted about 4 cc. of juice per hour. This would indicate the secretion of nearly 100 cc. daily from a small portion of the intestine containing duodenal glands.

The authors point out that the duodenal-gland-containing part of the intestine is the only part which gives an abundant secretion. The fact that the duodenal glands are histologically mucous glands tends to show that they are the source of the mucin of the juice. The high *p*H of the juice—much higher than the *p*H of jejunal juice—leads to the belief that the duodenal glands themselves are the source of much of the alkali found in the juice.

The work of Florey and Harding appears to add definite weight to the theory that a function of the duodenal glands is to protect, by reason of the alkali and mucin or mucinlike substances in the juice, the mucosa from injury by the acid chyme coming from the stomach. Numerous experiments in the pig by Florey and co-workers support this view. The duodenum was shown to possess a much greater resistance to gastric juice than is possessed by other parts of the intestine.

Comprehensive studies of the enzymic activity of duodenal juice obtained from duodenal fistulas in animals of several species (pig, dog, cat, rabbit, goat) showed the presence of amylase and enterokinase. Protease and peptidase were absent. Traces of invertase and lipase were sometimes found (Wright and co-workers).

The Control of the Secretion. In the cat and rabbit Florey and Harding have shown that secretion of the duodenal glands can occur independently of the extrinsic nerves. That a humoral control is present is indicated by the fact that the duodenum transplanted into the abdominal wall (cat) secretes when the animal is fed. Clearly in an experiment of this kind all nerve supply is abolished. Stimuli can reach the transplant only via the blood of the cutaneous vessels. Similar results have been obtained in pigs with duodenal transplants (Wright and co-workers). Evidence has been obtained which suggests that secretin is the humoral excitant for the duodenal glands (Florey and Harding, 1935b; Fogelson and Bachrach).

For the effect of the intestinal nerves on the secretion of the intestine, including the duodenal gland area, see p. 344.

BILE

The liver, the largest gland in the body, has a number of important functions which may be summarized as follows: (1) the secretion of bile; (2) the formation and storage of glycogen and the regulation of the glucose level of the systemic circulation; (3) the deamination of amino acids and the formation of urea; (4) the destruction of uric acid; (5) the synthesis of fatty acids from carbohydrate and protein, the phosphorylation of fats, the interconversion of the fatty acids, the partial oxidation of the fatty acids, and the formation of the ketone substances; (6) the formation of vitamin A from carotene and the storage of the vitamin; (7) the detoxication of poisonous substances brought to it by the blood; (8) aiding in the destruction of erythrocytes; (9) storage and distribution of the erythrocyte-maturing factor; (10) the formation of fibrinogen and probably other plasma proteins; (11) the formation of prothrombin; (12) the destruction of estrogens.

It is the present purpose to discuss the significance and secretion of bile. The other functions of the liver are dealt with in appropriate places.

The secretion of bile is therefore only one of many functions of the liver, and, as Mann (1927) pointed out, it is probably not its most important function in the higher animals.

Methods of Obtaining Bile. Bile may be obtained for study in a number of ways. Pavlov's method was to resect the bile duct and a small piece of intestinal wall surrounding it and to close the opening thereby made in the bowel. The piece of intestine containing the duct was then sutured into the abdominal incision, whereupon healing took place. As the bile passed to the outside through the fistulous opening, it could be collected for study. Since the gallbladder, which is present in most species used for experimental work, exerts in most cases a concentrating effect on bile, its removal may be necessary in certain biliary-fistula studies. Bile may be obtained from temporary fistulas of the hepatic ducts, the bile duct, or the gallbladder, and in other ways.

The Amount and Composition of Bile. According to the old studies of Bidder and Schmidt (cited by Vierordt) the daily amount of bile secreted per kilogram of body weight in different animals is as follows: cat, 14.5 gm.; dog, 19.9 gm.; rabbit, 136.8 gm.; sheep 25.4 gm. The recent studies of Schoregge on goats with bile fistulas indicate that the daily quantity varies from 24 to 30 cc. per kilogram of body weight. Quin (1936) obtained lower values for sheep. The average output of bile from a fistula of the bile duct of the horse is about 3000 cc. for a 20-hour period (Chiaravalle and Aramburn). Schmidt and Ivy have made a study of the amount of bile secreted in animals of many species.

The secretion of bile is continuous, although the rate varies with a number of conditions. In goats, according to the work of Schoregge, there is no night variation; the flow decreases with fasting and increases with feeding; rumination has no effect on the flow; administration of bile or hydrochloric acid into the duodenum increases the flow. In the horse secretion of bile continues during fasting but increases in amount during digestion.

Bile is a viscid, greenish, or golden-colored liquid with a bitter taste and a composition that is complex and that varies considerably in different species. The composition varies also depending upon whether bile is obtained from the gallbladder or from the ducts of the liver. In some species the gallbladder concentrates bile; that obtained from the gallbladder contains several times as much total solids as that obtained from the hepatic ducts directly (liver bile) and has a lower *p*H. The following constituents occur in bile: bile pigments, bile acids or bile salts, cholesterol, lecithin, a mucinlike substance, fats, soaps, urea, inorganic salts, and other substances. The accompanying table shows the chief constituents of liver bile of the dog (Rosenthal).

Specific gravity	1.008-1.015	
*p*H	7.4-8.5	
Dry substances	4.0	gm. per 100 cc.
Bilirubin	0.2-0.3	gm. per 100 cc.
Bile acids	2.0	gm. per 100 cc.
Fats, including lipoids	0.1	gm. per 100 cc.
Urea	0.03	gm. per 100 cc.
Iron	0.01	gm. per 100 cc.
Lime	0.025	gm. per 100 cc.

In the goat the specific gravity of bile varies from 1.004 to 1.010; dry matter, 2.88 to 4.72 per cent; ash, 0.48 to 0.76 per cent.

Bile Pigments. These are bilirubin and its oxidation product biliverdin. Bilirubin is present in the bile of all vertebrates and is the only pigment present in the bile of the dog. Biliverdin is found in the bile of many animals, especially the herbivores.

It has long been believed that hemoglobin is the source of bilirubin. This belief rests mainly on such evidence as the following: (1) the chemical relation of bilirubin to hemoglobin; (2) the formation of bilirubin at points of extravasation of hemoglobin; (3) the increase in bilirubin formation following any increase of free hemoglobin in the body. Mann and co-workers have brought forth additional evidence that bilirubin is formed from hemoglobin and that one of the intermediate products in its formation is hematin (heme). These investigators injected hemoglobin into the blood entering the spleen and bone marrow and found that the blood leaving these organs contained an increased amount of bilirubin. It may therefore be concluded that bile pigment is derived from blood hemoglobin. The question arises whether muscle hemoglobin is also a source of bile pigment. Hawkins and

Johnson have expressed the belief that under normal conditions one-third to one-fourth of the bile pigment eliminated daily comes from muscle hemoglobin, the rest from blood hemoglobin.

The stages in the formation of bilirubin from hemoglobin are not fully understood. As stated above, hematin (heme) appears as an intermediate product. This is the pigmentary portion of the hemoglobin molecule and contains iron, whereas bilirubin is iron-free. In some way, therefore, iron is split off and the remainder of the pigment is converted to bilirubin. The iron-containing fraction is largely conserved by the body to be used again in the formation of new hemoglobin (p. 33). About 30 per cent of the iron of the body is found in storage depots.

The question of the place of bilirubin formation has been actively studied. In view of the fact that bilirubin is eliminated in the bile and that the latter is a product of the liver, it might be supposed that bilirubin is formed in the liver. Present evidence indicates that some of the bilirubin is of liver origin. However, observations by a number of investigators (Mann, 1927) show that when the liver of the mammal is removed, bile pigment, as indicated by the appearance of a yellow coloration in the blood plasma and tissues, continues to be formed. The most convincing evidence that the pigment which continues to develop in dehepatized animals is bilirubin is furnished by the experiments of Mann, Sheard, and Bollman, who identified the pigment by means of the spectrophotometer. There is therefore no doubt that some bilirubin is formed outside the liver. Research has shown that the extrahepatic sites of bilirubin formation are the spleen and bone marrow. Of the three known sites of bilirubin formation, the bone marrow is the most important and the liver the least. The evidence indicates that the reticulo-endothelial cells in the locations just indicated are the actual places of the transformation of hematin into bilirubin.

As far as is known, the bile pigments are waste products of the metabolism of hemoglobin and are without further use to the body. They enter the intestine as a part of the bile and are mixed with the ingesta. During their passage along the bowel, they become reduced by bacterial action and appear in the feces, not in their original form, but in the form of urobilin (stercobilin). The brown color of the feces is due principally to this substance (but to some extent to pigments of food origin). It was formerly believed that the bile pigments were in part absorbed from the intestine into the portal blood and returned to the liver, where they were again eliminated, but recent work on dogs (Bollman, Sheard, and Mann; Blankenhorn) shows that no such absorption of bilirubin occurs. However, its absorption by the lymphatics might occur in minute amounts. As regards urobilin, Blankenhorn was able to show that it is absorbed by both the portal blood and the lymph. The absorbed urobilin is largely re-eliminated into the intestine by the liver, but some of it is excreted by the kidney.

Bile Salts: Bile as a Digestive Secretion. The bile salts are the solium—and to a lesser extent the potassium—salts of glycocholic and taurocholic acids, formed in the liver and found in bile. In carnivorous mammals and in birds taurocholic acid prevails; in the sheep and goat the same acid predominates. In the ox sometimes one is in excess, sometimes the other. In the rabbit, hare, and pig, glycocholic acid is present almost exclusively (Hammersten and Hedin). Taurocholeic and glycocholeic acids, similar in composition to the foregoing, have been described in small amounts in certain biles.

Glycocholic acid ($C_{26}H_{43}NO_6$) is a compound of glycine and cholic acid, as may be shown by hydrolyzing it with acid. Taurocholic acid ($C_{26}H_{45}NSO_7$) is a compound of taurine and cholic acid. Glycine and taurine are of protein origin. Glycine is the simplest of the amino acids, is widely present in the proteins of the foods and tissues and can be synthesized by the body. Taurine, a sulfur-containing, nitrogenous substance, is derived from the amino acid cystine and may possibly be a normal intermediary product of cystine metabolism. Cholic acid, which has the formula $C_{24}H_{40}O_5$, is derived from cholesterol. This has been shown by an experiment in which the injection into a dog of cholesterol labeled with deuterium resulted in the formation of cholic acid that contained deuterium (Bloch, Berg, and Rittenberg).

Bile is both an excretion and a digestive secretion. It is chiefly because of the presence of bile salts that bile is able to function in the latter way. The value of bile as a digestive secretion was mentioned in connection with pancreatic digestion. Bile, by reason of its bile salts, is of use in digestion and absorption in the following ways: (1) Bile activates pancreatic lipase. (2) Bile probably accelerates slightly the action of pancreatic amylase. (3) Bile assists in fat emulsification. (4) The higher fatty acids are nearly insoluble in water, but in the presence of bile their solubility is increased. Thus their absorption is aided. When bile is not allowed to enter the intestine, fat absorption is definitely decreased (Coffey, Mann, and Bollman, 1940b). During fat absorption the bile salts are also absorbed, in combination with the fatty acids. The reabsorbed bile salts thus enter the portal blood and are carried back to the liver, where they are again excreted. This constitutes the so-called circulation of the bile salts. During their re-elimination they act as cholagogues, or stimulants to the flow of the bile. The absorption of bile salts from the intestine is not quantitative; consequently they are lost to some extent from the body in the feces. However, the loss in this way is small. (5) Bile assists in the absorption of the fat-soluble vitamins.

Bile has some importance as a digestive secretion aside from its content of bile salts. (1) It is a reservoir of alkali and thus assists in maintaining an optimal reaction in the intestine. (2) The mucin or mucinlike constituent of bile and the protein of pancreatic and intestinal juices act as stabilizers of the fat emulsion in the intestine. (3) Bile was formerly believed to have marked antiseptic properties and thus to regulate bacterial growth in the bowel. This view was based largely on the observation that when bile does not enter the intestine the feces develop a very offensive odor, because of intestinal putrefaction. That bile is itself not a general antiseptic of importance, however, is indicated by the fact that it can serve as a culture medium for many microorganisms. The known antiseptic action of bile in the intestine must therefore be less direct, and is explained as follows: When bile does not enter the intestine fat absorption is diminished, and the other food constituents become coated with a film of fat or fatty acid. For this reason their digestion is hindered, and in the case of protein putrefaction occurs. The feces therefore develop an offensive odor. Bile also has a moderately laxative effect. The digestive functions of bile are discussed in a review by Schmidt.

Cholesterol. Occurring in significant amounts in the bile of practically all animals, cholesterol belongs to the group of lipids known as sterols. Cholesterol is found not only in bile but also in blood and other body liquids. In the blood it may occur in the free form or esterified with fatty acids, whose transport it probably aids. It is universally present in the cells of the animal body, is believed to be of importance in regulating the permeability of their peripheral membranes, and may be of use in other ways. It is an important constituent of the stroma of red blood corpuscles and is present in large amount in the white matter of nerves. It is closely related to the steroid compounds such as the adrenal and sex hormones, vitamin D, and the bile acids.

Cholesterol is formed in the liver for use in the metabolic processes. Cholesterol in excess of the body's needs is eliminated in the bile. Cholesterol does not occur in plants, but it is present in most animal fats. In carnivorous animals, therefore, some of the cholesterol of the bile is probably of food origin. Some of the cholesterol entering the intestine with the bile is reabsorbed from the intestine. The rest appears in the feces after having undergone modification by bacteria in the intestine.

Cholesterol is often the chief constituent of gall stones. It would be insoluble in bile were it not for the bile salts. It is probable, therefore, that a decrease in bile salts is a factor in the settling out of cholesterol to form gall stones (Oliver). Pathological deposits of cholesterol may occur elsewhere in the body.

The Secretion of Bile. Bile is secreted continuously by the hepatic cells; however, the rate varies with the food and other factors. Although the liver possesses an abundant efferent nerve supply, the evidence is against the idea that the nerves are secretory; their main function seems to be vasomotor. Drugs stimulating the sympathetic and the parasympathetic are without effect on the secretion of bile. If the liver does not possess secretory nerves, what constitutes the stimulus for the secretion of bile? It is possible that a humoral mechanism is concerned, or it may be that the production of bile is dependent merely upon variations in the volume and pressure of the blood flowing through the liver. Experiments made in an effort to test the latter possibility have not yielded conclusive results (Downs; Tanturi and Ivy). Probably there is some relationship between blood flow and bile output. As to the first possibility, a number of observations make it likely that a humoral mechanism is concerned, and it is believed that bile salts and secretin absorbed from the intestine are the excitants. The production of bile under the influence of stimuli coming from the seat of most active digestion (small intestine) would thus be co-ordinated with the needs of the digestive organs.

The pressure under which bile is secreted has been studied by Mann and Foster in a number of animals, some possessing gallbladders (goat, rabbit, guinea pig, striped gopher) and some not (rat, pocket gopher), and it was found that variations of considerable magnitude occurred in the different species (goat, 182 mm. bile; rabbit, 265 mm. bile; guinea pig, 203 mm. bile; striped gopher, 125 mm. bile; pocket gopher, 147 mm. bile; rat, 215 mm. bile), but that the presence or absence of a gallbladder was not one of the causes of the variations. In goats the secretory pressure is, according to Schoregge, about 270 mm. bile. In sheep Rangsit found an average bile secretory pressure of 216 mm. bile.

The Extrahepatic Biliary System. The hepatic ducts, the gallbladder and its cystic duct, and the bile duct constitute the extrahepatic biliary tract. There are marked anatomical variations in this system in different species (Mann, Brimhall, and Foster). Animals of most species possess a gallbladder, although it is lacking in some. The horse, deer, and rat are familiar animals that do not have a gallbladder, and it is a remarkable fact that one species of gopher (striped gopher) has a gallbladder whereas another species (pocket gopher) has not. Even more striking is the fact that in the giraffe it is sometimes present and sometimes absent. Marked variations occur in different species in the relation of the bile duct to the pancreatic duct (Mann, Foster, and Brimhall).

As previously stated, bile is secreted continuously by the liver but at a variable rate. Its entrance into the bowel in animals possessing a gallbladder is intermittent; in animals not possessing a gallbladder, continuous (Giordano and Mann). During the time bile is not flowing into the intestine it is stored in the gallbladder. It has been shown in goats that bile does not remain in the gallbladder long and that liver bile may flow directly into the intestine for hours (Schoregge). The discharge of bile into the intestine and the filling of the gallbladder are controlled by a muscular mechanism at the duodenal end of the bile duct. In animals not possessing a gallbladder, the resistance to the passage of bile from the bile duct into the duodenum is low, whereas in animals possessing a gallbladder the resistance is higher.

The gallbladder periodically discharges its contents into the intestine by contraction of the muscular tissue in its wall. Motility of the gallbladder is apparently little affected by the extrinsic nerves, but that a hormone mechanism is concerned is evident from the work of Ivy and Oldberg. They demonstrated that the mucosa of the upper part of the small intestine produces a hormone which causes the gallbladder to contract and evacuate. The name *cholecystokinin* has been given to the hormone.

The nerves of the gallbladder are the vagi and splanchnics. The vagi are predominantly motor, the splanchnics predominantly inhibitory. However, as noted above, the extrinsic nerves apparently play only a minor part in gallbladder motility.

Other factors concerned in emptying the gallbladder are (1) the washing out of its contents by bile coming from the liver, (2) the elasticity of its wall and the variations in intra-abdominal pressure, and (3) the absorption of some of the biliary contents by the wall of the gallbladder.

The gallbladder in some species of animals exerts a concentrating action on the bile entering it. The pigment concentrations in bladder bile and liver bile give a basis for judging the concentrating action. Water and inorganic salts are the principal substances absorbed. The following animals, among others, have gallbladders capable of considerable concentrating effect (5 to 10 times) on bile: cat, dog, rabbit, mouse, chicken, man. These animals have gallbladders with little or no concentrating ability: pig, sheep, goat, cow (Schmidt and Ivy).

Summary of the Functions of the Gallbladder. (1) In some species (cat, dog, rabbit, mouse, chicken, man, and others) the gallbladder stores bile, presumably for use later on in digestion and absorption. In these same animals the gallbladder concentrates bile. This enhances its function as a reservoir and may be useful in other ways. (2) The gallbladder has a pressure-regulating function, acting as an elastic bag in a system of relatively inelastic tubes. In this way extreme variations of pressure in the system of biliary ducts is minimized. This is apparently the only function of the gallbladder in the pig, sheep, goat, and cow. (3) The gallbladder adds mucin or a mucinlike substance to bile. One of the functions of this substance may be to delay the absorption of bile salts from the intestine, thus preventing hemolysis in the portal blood. Another function may be to assist in stabilizing the fat emulsion formed in the intestine. The functions of the gallbladder are reviewed by Mann (1924) and Ivy (1934).

REACTION IN THE INTESTINE

Gastric juice is acid in reaction, whereas duodenal juice, pancreatic juice, bile, and often intestinal juice as well, are alkaline in reaction. Absorption is an important process in the intestine. One would expect therefore that the reaction of the intestinal contents would vary somewhat in different places and at different times. Myers and McClendon studied the reaction of the duodenum of man by means of the duodenal tube and usually found that the reaction three to four hours after meals fluctuated around the neutral point, but that the extreme acidity was greater than the extreme alkalinity. Graham and Emery found that the reaction in the duodenum of the dog varied from *p*H 6.2 to 6.5 regardless of whether the dogs were fed a normal diet or one in which protein, fat, or carbohydrate predominated. From the duodenum to the ileocecal valve the reaction became gradually more alkaline. It was acid in the cecum. McClendon and co-workers expressed the belief that the reaction of the intestine is determined more by the relative length of the intestine than by the character of the food. Grayzel and Miller likewise found that diets high in fat, protein, or carbohydrate caused no notable change in intestinal reaction in dogs.

Continual adjustment of the reaction of the intestinal contents goes on. Changes in the bicarbonate concentration and carbon dioxide tension in the contents are important factors in the adjustment.

Leasure, Link, and Whitlock made observations on the reaction of various parts of the gastro-intestinal tract of aged horses killed at a horse-slaughtering establishment. The determinations were made shortly after the death of the animals. The following average results were obtained: stomach, *p*H 4.46; duodenum, *p*H 7.13; jejunum, *p*H 7.47; ileum, *p*H 7.55; cecum, *p*H 7.24; large colon, *p*H 7.09; rectum, *p*H 6.24.

Chapter XVI

DIGESTION IN THE LARGE INTESTINE; INTESTINAL MOVEMENTS

MATERIAL that escapes absorption in the small intestine is gradually propelled through the ileocecal valve into the large intestine. The nature of this material varies greatly in carnivores and herbivores, and because of this the significance of the large intestine is different in these animals.

THE LARGE INTESTINE OF CARNIVORES

From the standpoint of actual digestion carnivores have little need for a large intestine; digestive processes are practically complete in the small intestine. The functions of the large intestine are mainly to return to the blood water that has been poured out by the digestive glands, and to act as a reservoir for the waste materials that constitute the feces. The latter are expelled at intervals from the bowel by the act of defecation.

Form and Structure. The colon of carnivores is relatively short and is nonsacculated; the cecum is poorly developed. Intestinal glands are found throughout the large intestine, but their secretion is different from that in the small intestine. No villi are found in the large intestine.

Secretion. The glands of the large intestine are mainly mucous glands and do not produce enzymes. Such enzymes as are found there are carried down from the small intestine with the ingesta. The secretion of the large intestine is a mixture of the secretion of the surface epithelium and of the gland cells, and is clear, viscid, and highly mucous. It is alkaline in reaction and contains mucous flakes and cell fragments.

From isolated colonic loops(dogs) with intact blood, lymph, and nerve supplies, de Beer, Johnston, and Wilson obtained a secretion which had, when the results are averaged, 1.30 per cent of solids, 0.89 per cent of ash, and a *p*H of 7.99. The rate of secretion was less than in jejunal and ileal loops.

Stimulation of the peripheral ends of the nervi erigentes in the cat causes a secretion of fluid by the colon (Wright, Florey, and Jennings).

Bacterial Action. Conditions in the small intestine of carnivores and of man are not favorable to extensive bacterial action. In the large intestine, on the other hand, the environment is such that bacteria multiply and act easily. They are numerous and are chiefly of the putrefactive type, attacking such protein and its split products as may have escaped digestion and absorption in the small intestine. The best-known products of this attack are indole, skatole, paracresol, and phenol. However, volatile fatty acids, hydrogen sulfide, histamine, tryamine, and other substances may be present. In addition, products similar to those formed by the action of proteolytic enzymes may result when putrefaction is not too extensive.

Some of the putrefactive products mentioned above may be absorbed into the portal blood and carried to the liver. It has long been supposed that, to the extent that they escape detoxication or destruction in the body, they might prove toxic to the organism. Yet the intestinal mucous membrane and the liver itself act as barriers against the extensive entrance of these substances into the general circulation, and it is probable that their harmful influence has been greatly overestimated (Alvarez, 1924). It has been shown that, in some people, packing the rectum with cotton can produce the classical symptoms of autointoxication, the effect of the pack being due to reflexes from the lower bowel. The prompt relief afforded by a bowel movement in so-called autointoxication is probably due more to the mechanical effect of emptying the rectum and the consequent withdrawal of reflexes from this, in many individuals, very sensitive part of the bowel than to the removal of toxic substances.

Indole, derived from bacterial attack on the amino acid tryptophane, is detoxicated in the liver and probably elsewhere and is excreted in the urine. Detoxication consists in a preliminary oxidation to indoxyl, which is then conjugated with potassium sulfate to form indican. The amount of indican in the urine affords a rough index of the extent of intestinal putrefaction.

Skatole (methyl indole) behaves similarly in the organism to indole, though it is absorbed only in traces and is less toxic. The odor of feces is due chiefly to indole and skatole.

Phenol is formed in the bowel, probably from the amino acid tyrosine, and is eliminated to a considerable extent in the feces. However, a part of it is absorbed and this is excreted largely unchanged in the urine, although some conjugation with potassium sulfate occurs in the liver and elsewhere in the body. The defenses of the body against phenol appear to be very well developed.

Paracresol, similar to phenol, occurs in the urine conjugated with potassium sulfate.

It may be pointed out at this time that these substances, the phenols and indoles, are not derived exclusively from putrefaction in the intestine; they are also formed in the normal metabolism of certain of the amino acids. Those so formed are detoxicated similarly to the ones derived from putrefaction in the intestine.

THE LARGE INTESTINE OF HERBIVORES

From the standpoint of digestion and absorption the large intestine of herbivores is of great importance. This is especially true in animals with simple stomachs such as solipeds, the rabbit, and the guinea pig. In all herbivorous mammals a digestive tract with a roomy compartment somewhere in its course is necessary for the maceration, fermentation, and solution of the fibrous portions of the food. In ruminants such a compartment is provided principally in the rumen; in simple-stomached animals the enormous cecum and colon meet this requirement. However, cellulose digestion is not the sole function of the large intestine in simple-stomached herbivores. The digestion of other products occurs, and much absorption must take place.

Form and Structure. The cecum and colon of simple-stomached herbivores are relatively very capacious, and are sacculated. In ruminants, however, they are relatively small and are nonsacculated. As in carnivores and omnivores, so in herbivores, glands are present throughout the large intestine and villi are absent.

Secretion. Very little information is available regarding the secretion of the large intestine of herbivores. Histological studies indicate that the glands are mainly mucous. It is doubtful whether they produce any enzymes of much consequence in digestion, the secretion probably having essentially a physical function.

Digestive Processes. A considerable part of the food of herbivorous animals, especially those possessing a simple stomach, reaches the large intestine in a form not yet ready for absorption. Further digestive changes of a chemical nature are brought about in the material by enzymes carried down from the small intestine, by bacteria, and possibly by protozoa. The enzymes carried down with the food produce in the large intestine changes characteristic of their action elsewhere.

Bacterial action in the large intestine is of both fermentative and putrefactive types. Fermentation affects mainly the carbohydrates. The digestion of cellulose and other carbohydrates in the large intestine yields products similar to those produced by their digestion in the rumen, namely, lower fatty acids (p. 326). They are absorbed and utilized by the animal. The investigations of Elsden and co-workers show that large amounts of volatile acids occur in the cecum and colon of ruminants, the horse, and the pig. This indicates that much fermentation of carbohydrate takes place in these locations. Lower fatty acids are found in significant amounts in the blood draining the cecum and colon of herbivores (Barcroft, McAnally, and Phillipson, 1944b). This indicates absorption (p. 388). Putrefaction of protein occurs to some extent in the large intestine of herbivores.

The gases of the large intestine are in part expelled through the anus and in part absorbed into the blood and eliminated through the lungs. They comprise not only carbon dioxide and methane but also small amounts of hydrogen and oxygen as well as a considerable quantity of nitrogen (goats, 14 to 51 per cent N_2, according to the work of Washburn and Brody).

The Rate of Passage of Residues. The time required for the passage of food residues through the digestive tract of herbivorous animals may amount to several days. In simple-stomached herbivores most of this time is spent in the large intestine.

DIGESTIBILITY OR DIGESTION COEFFICIENT

As here used, the term digestibility refers to the extent to which a food is digested. It is usually expressed as a percentage. When so expressed it is referred to as the digestion coefficient of the food. An example may be given. For every 100 grams of protein in alfalfa hay consumed by a steer, 71 grams apparently undergo digestion and absorption. The digestion coefficient of protein in alfalfa hay for steers is therefore 71. In the determination of digestion coefficients a digestion trial is run. This involves a determination of the weight of the food consumed and of the feces voided over a certain period, and an analysis of samples of the food and feces for dry matter and other substances (protein, ether extract, crude fiber, N-free extract, and ash). Then by subtracting outgo from income a difference is obtained which, expressed as a percentage, represents the apparent digestibility, or digestion coefficient, of the food or some constituent of it. A preliminary feeding period of several days is necessary in herbivores in order to expel residues of previous foods from the alimentary tract.

It should be added, however, that because certain principles (nitrogenous substances, ether extract, and ash) found in the feces are not derived exclusively from the food but arise in part as products of metabolism eliminated by the intestine, corrections may have to be made for these lest the results of digestion experiments be too low. In practice a correction is often made for the metabolic nitrogen in the feces, and ash determinations are usually omitted entirely. A correction for crude fiber is unnecessary because it is clearly not a product of metabolism, and substantially the same thing applies to other carbohydrates (nitrogen-free extract). A correction for ether extract (crude fat) may be omitted without serious error.

The digestibility of a foodstuff varies with a number of factors such as the nature of the food of which it is a part, the individuality of the animal, and the species. Thus the crude protein of flaxseed is more digestible than that of oats, the crude fiber of dent corn is more digestible than that of wheat bran, and crude fiber in general is more digestible by ruminants than by other herbivorous animals. The digestibility of the food of carnivores and of man is, as one would expect, very high; of herbivores, comparatively low, because of the large amount of crude fiber present.

The accompanying table shows the digestion coefficients of several common foods for ruminants, horses, and swine.

DIGESTION COEFFICIENTS
(HENRY AND MORRISON)

Animal	Food	Dry Matter	Crude Protein	Fiber	N-free Extract	Fat
		per cent	*per cent*	*per cent*	*per cent*	*per cent*
Ruminants	Corn, ground	90	74	57	94	93
	Corn-and-cob meal	79	52	45	88	84
	Cottonseed meal	77	84	37	75	95
	Wheat bran	65	78	31	72	68
	Hay from mixed grasses	61	55	63	62	48
	Hay from alfalfa	60	71	43	72	38
Horses	Corn	74	58		83	48
	Oats		80	29	75	71
	Timothy hay	44	21	43	47	47
Swine	Shelled corn	87	75	44	92	64
	Wheat middlings (shorts)	82	83	30	86	83
	Barley		77	12	89	44
	Soybean meal		84	30	100	84

From this table it is seen that, with few exceptions, the constituents of vegetable foods are not completely digestible by farm animals. As previously stated, this is due largely to the crude fiber present, and in general it may be stated that the digestibility of the different foodstuffs is inversely related to the crude-fiber content of the food. The way in which crude fiber lowers the digestibility of other foodstuffs is as follows: Crude fiber itself is only partially digestible even by ruminants, largely because of the lack of time for its complete fermentation as it passes through the alimentary canal. Hence considerable amounts of foodstuffs such as starch and protein, which are intrinsically quite digestible, are not completely digested owing to their imprisonment in a cellulose covering. The failure of complete digestion of cellulose results therefore in a failure of complete digestion of certain intrinsically digestible substances, and copious feces result. The digestibility of foods by dogs is high (Coffey, Mann, and Bollman, 1940a).

THE FECES

The term feces refers to the waste matter voided from the bowel through the anus by the act of defecation. The feces are composed of water; indigestible and undigested food residues; remains of digestive secretions such as bile acids, bile pigments, and mucin; desquamated epithelial cells, derived from the digestive tract; numerous bacteria. many of which are dead; inorganic salts in great variety, some of which are derived by excretion through the large intestine; indole and skatole, which give the feces their characteristic odor; and other substances. The water content of the feces varies considerably in the different animals, as follows: sheep, 68 per cent; cow, 83 per cent; horse, 75 per cent; pig, 80 per cent (Stutzer). The difference in the water content of the feces of the sheep and the cow, both ruminants, is remarkably great. The reaction of the feces of normal horses is acid and lies between *p*H 6.5 and 6.8 (Pötting).

From the foregoing considerations it is evident that the feces are to be regarded as composed essentially of excretory products and food residues. In carnivores, and in man when on a concentrated diet. the amount of food residue is small, digestion and absorption being nearly complete. The solid matter of the feces in such cases is composed, therefore, largely of excretory products. On the contrary, in herbivores, and to a lesser extent in swine, the feces contain large amounts of food residues and relatively small amounts of excretory products. The large amount of food residue in the feces of these animals is explained by the high crude-fiber content of their foods.

The Amount of Feces. The amount of feces varies with the amount and kind of food and is relatively much greater in herbivores than in carnivores. The daily amount of feces for the horse is 15 to 23 kg. The ox when fed for maintenance and low production eliminates 13 to 35 kg. daily; when fed for fattening, 40 to 45 kg., or more. Sheep produce 1 to 3 kg. Swine produce 0.5 to 2.5 kg., depending upon the food (Ellenberger and Scheunert).

Fuller found that the average daily amount of feces produced by dairy cows was 59 pounds (27 kg.) per 1000 pounds of live weight.

INTESTINAL MOVEMENTS

The intestine is the seat of several kinds of movements whose functions are (1) to mix the ingesta with the digestive secretions, (2) to bring the digested products into contact with the intestinal mucous membrane for absorption, (3) to move the food mass from place to place in the bowel, (4) to expel the residue from the rectum through the anus, and (5) to assist in the flow of blood and lymph through the vessels of the intestinal wall.

Local stretch of the gastro-intestinal wall by some of the ingesta is the principal stimulus which starts the contractions that mix the ingesta or propel them to a new location.

The flow of liquids along the alimentary canal is governed by basic physical laws. Intraluminal pressure gradients are necessary for the passage of ingesta along the digestive tract. If no difference of pressure exists, no movement of material will occur. Activity of the gastro-intestinal musculature provides the necessary pressure or force, but the ways in which this force manifests itself may differ in the transport of liquids and solids.

Intestinal motility has been extensively studied in the small domestic mammals, both carnivorous and herbivorous, and in man. Knowledge of the movements in swine, solipeds, and ruminants, however, is relatively limited. The methods of studying intestinal movements are similar to the methods of studying stomach movements (p. 295). In addition special methods have been developed.

Movements of the Small Intestine. At least the following kinds of motor activity are recognized in the small intestine: rhythmic segmentations, pendular movements, peristaltic rushes, slowly traveling peristaltic waves, tonus waves, tonus rings, and antiperistalsis. The relative importance of these different types of motility is not the same in all species.

Rhythmic Segmentations. This type of movement has been carefully studied by Cannon (1911). It is the most common to be found in the small intestine, at least of the cat and dog. A mass of food lying quietly in a portion of the intestine is, by constrictions at fairly regular intervals along the mass, suddenly cut into small ovoid pieces. These are then immediately cut in two by constrictions near their middle, and the adjacent pieces are rushed together. Other contractions follow at once, severing these newly formed segments, and the process is repeated. Both muscle coats are involved in rhythmic segmentations. The process may be going on in several parts of the small intestine simultaneously. Periods of segmentation frequently last for more than thirty minutes. The rate of segmentation in the cat is commonly as high as 28 to 30 a minute; in the dog, 18 to 22 a minute or at other times 12 to 14. Rhythmic segmentations are less common in the rabbit.

The main effect of segmentations seems to be to mix the food with the digestive juices and to bring it into contact with the mucosa for absorption. The segmentations doubtless also assist in the flow of blood and lymph through the intestine. They contribute somewhat to the movement of intestinal contents along the bowel, apparently by traveling at a slow rate.

Pendular Movements. These are common in the rabbit. They also occur in man, the horse, the sheep, and other animals. Pendular movements are in some respects similar to the rhythmic segmentations, and are, as the name implies, swinging or swaying in type. The wall of the bowel seems to be pulled over the contents first in one direction and then in the other. This type of motor activity slowly travels down the bowel (Alvarez, 1940). Pendular movements when very active are believed to give origin to peristaltic rushes.

Rhythmic Contractions in Isolated Segments. If small segments of intestine are removed from the body and suspended in warm, oxygenated Locke's solution, they will contract rhythmically, or beat, for a long time. Graphic records of the contractions can be obtained by anchoring one end of the segment and attaching the other end by a thread to a light lever arranged to write on a kymograph (Fig. 80, p. 297). The rhythmic contractions so observed and recorded are related to, or are a manifestation of, the rhythmic segmentations and pendular movements just described as occurring in the intact bowel.

By using this technic it is possible to demonstrate a gradient of rates of rhythmic contraction in the intestine. As regards the small bowel, the most rapidly contracting segments are obtained from the duodenum; the least rapidly from the ileum. The average rates as determined from four places in the small intestine of the chicken are: duodenum, 10.4 beats per minute; upper ileum, 9.3; middle ileum, 8.1; lower ileum, 6.0 (Orr). Some of the individual results are shown graphically in Fig. 97. This gradient is probably one of the factors determining the direction of peristaltic rushes, as noted below.

Rhythmic Contractions in Exteriorized Loops of Intestine. Loops of intestine in continuity with the bowel may be brought to the surface and permanently enclosed in tubes of skin. It is possible to prepare such loops at different levels of the bowel. The motor activity of the loops can be studied. In dogs rhythmic contractions in exteriorized loops of small intestine are not common; other types of motility prevail.

Rhythmic contractions, when present, occur at a constant rate in a given loop. There is a gradient of rates of rhythmic contraction, the loop nearest the pylorus having the highest rate, the one at the lowest level in the intestine having the lowest rate. The gradient is evident in the following data (averages) obtained from dogs (Douglas and Mann): jejunum, 6 inches below ligament of Treitz, 18.0 rhythmic contractions per minute; ileum, 30 inches above cecum, 13.9 contractions; ileum, 25 inches above cecum, 13.8; ileum, 10 inches above cecum, 13.4; ileum, 4 inches above cecum, 12.5.

Peristaltic Rushes. These are rings of contraction which rapidly widen posteriorly so that a considerable length of intestine becomes constricted; both coats of muscle are involved. Following the wave of contraction there is a wave of relaxation running in the same direction, the intestine remaining flaccid for some time after its passage. The peristaltic rush usually propels a column of ingesta.

Bayliss and Starling (1899), in their classical studies on peristalsis in dogs, claimed that there is an area of relaxation ahead of the ring of contraction and that the bowel contents are pushed into this relaxed area. They formulated their *law of the intestine* on the observation that a stimulus at any point in the intestine caused contraction above and inhibition below the point. Cannon designated this local response as the myenteric reflex. Alvarez and Zimmermann, working with rabbits, failed to show, by means of tracings and motion pictures, the presence of relaxation ahead of the peristaltic rush. Any dilatation that could be detected was due to distention of the intestine by the advancing column of ingesta. Henderson likewise adhered to the view that there is no actual relaxation of the bowel ahead of the peristaltic wave. This so-called law of the intestine apparently has limited application.

Alvarez (1928) has shown (rabbits) that the length of the column of ingesta pushed by the wave of peristalsis is ordinarily about 36 cm., and its average rate of travel about 6 cm. a second. This means ordinarily that the wave is traveling at the same rate. The farther the wave goes, the faster it travels. Following the passage of a peristaltic wave, the bowel may remain contracted for 10 to 25 seconds, during which time the rush is still in progress and the head of the column of ingesta advances 60 to 150 cm. Some rabbits show several rushes an hour; others only a few during a day.

The effect of the peristaltic rush is usually to carry ingesta down the bowel, but Alvarez and Mahoney (Alvarez, 1928) have shown that at times there may be no relation between the wave of peristalsis in the muscular wall of the bowel and the movement of ingesta inside the tube. Usually the wave carries ingesta ahead of it, but at times it passes on over its load, leaving the load behind. Liquids may pass along the bowel for considerable distances in the absence of rushes. Other muscular activity of the bowel supplies the force.

The intestine is *polarized*. It transmits its contents more readily downward than upward. The normal direction of the peristaltic rush is down the intestine. Probably the best explanation of the polarity of the bowel is found in the gradients that exist in its wall. Some of the activities of the intestine that have been shown to be graded are rate of rhythmic contraction, tone, irritability, and latent period. Graphic representations of two of these gradients are shown in Figs. 97 and 98. Some of these gradients are probably dependent upon an underlying gradient of metabolism in the wall of the intestine, the upper part of the intestine having a higher metabolic rate than the lower (Alvarez and Starkweather).

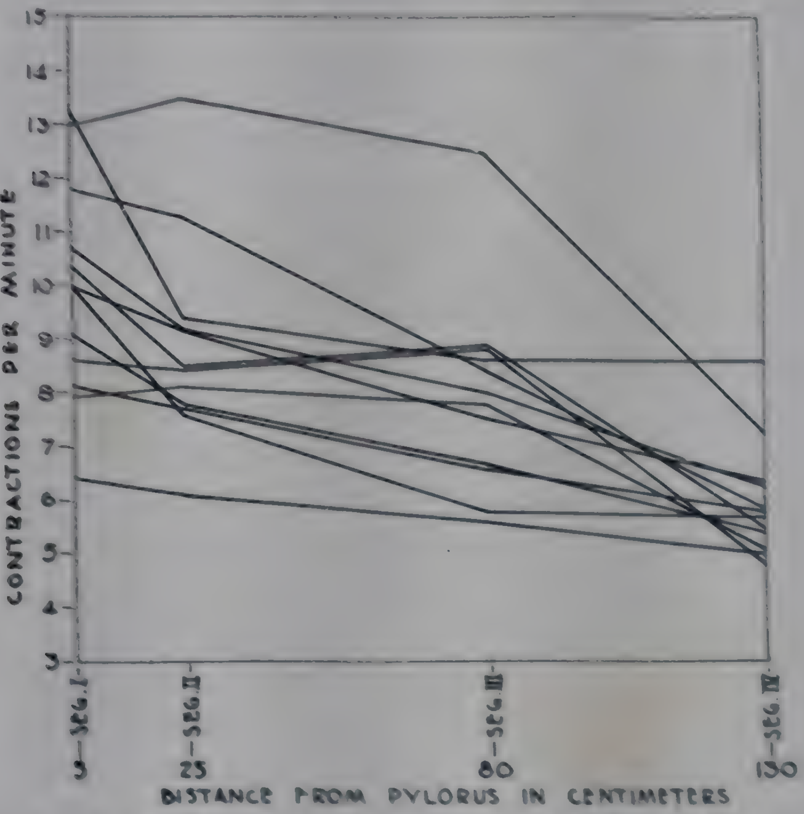


FIG. 97.—A gradient of rate of rhythmic contraction in isolated segments of the small intestine of the chicken. Four segments were used from each bird. They were obtained from places in the small intestine that were 5, 25, 80, and 130 cm., respectively, from the pylorus. The lines connect rates of contraction in one bird. (Data of H. W. Orr.)

Peristaltic rushes can begin anywhere in the bowel and can run short or long distances down the bowel. According to Alvarez about 55 per cent (rabbit) start in the duodenum about the time a peristaltic wave in the stomach reaches the pylorus. Emptying of stomach contents into the duodenum is not necessary to start a rush. According to Henderson slight increases in pressure in the bowel may be enough to start a wave of peristalsis. Distention caused by the presence of ingesta in the bowel is the usual way of giving rise to a rush. Most of the rushes in the small intestine of the rabbit disappear in the ileum; some may go on to the colon, frequently giving rise to contractions of the cecum as they pass. Those that stop in the ileum either fade out or are stopped by strong contractions or rises of tonus. Alvarez regards the stopping of rushes as one of the important functions of the ileocecal sphincter and of the slight rise in the gradient just before the sphincter is reached. That many of the rushes are stopped is fortunate; otherwise diarrhea would be very common.

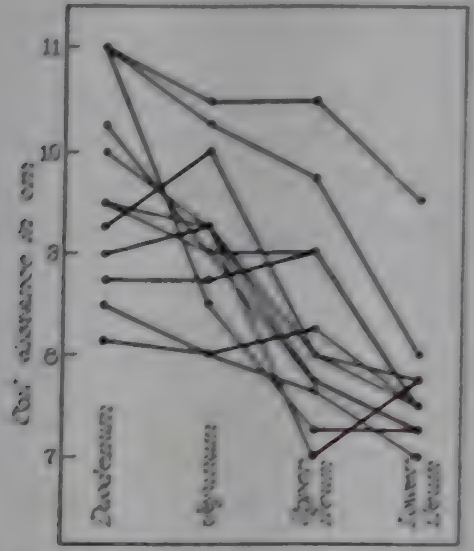


FIG. 98—A gradient of irritability in the small intestine of the rabbit. Ordinates represent the threshold for faradic stimulation as measured by the distance between the primary and secondary coils of an inductorium. The greater the irritability, that is, the lower the threshold, the greater is the coil distance. Abscissas represent four different regions in the small intestine. The lines connect readings in one animal. (From Dukes, *Proceedings of the Society for Experimental Biology and Medicine*, 1929, 27.)

Slowly Traveling Peristaltic Waves. These have been observed particularly in dogs. They travel slowly, only about 1.5 cm. a minute. Not a great deal is known about them. They are propulsive contractions.

Tonus Waves. These are slow changes in the length of the muscle fibers of the intestinal wall. They may exist alone or may show superimposed rhythmic contractions. Both muscular coats of the bowel may be involved. Tonus waves appear to be involved in starting and stopping rushes but do not seem to travel along the bowel (Alvarez).

Tonus Rings. These are strong local contractions of the circular musculature of the intestine. They appear often to be concerned in stopping peristaltic rushes. They may pulsate.

Antiperistalsis. Peristalsis in the oral direction has been designated as antiperistalsis or reverse peristalsis. This movement, formerly thought to be limited to the large intestine and to the stomach in vomiting, is now believed to be possible practically anywhere in the gastro-intestinal tract. It is of course neither so widespread nor so powerful as peristalsis in the aboral direction, otherwise food would not go down the bowel. To what extent it is a normal feature in the small intestine is uncertain, but that it can occur is undoubted. Its usefulness may be to delay the movement of food down the bowel, to insure adequate mixing of the food with the digestive secretions, and to make possible the regurgitation of duodenal contents into the stomach. Reverse peristalsis may occur in certain gastro-intestinal disorders.

Movements of the Large Intestine. The movements of the large intestine are, generally speaking, more sluggish than those of the small. This is in keeping with its function as a reservoir for fecal matter or as a place for prolonged bacterial attack on cellulose and other substances. Nevertheless, the contractions at times may be be very powerful. Thus effective propulsion is brought about.

Colon. The colon shows at least three kinds of motor activity: peristalsis, reverse peristalsis, and contractions of the haustra, or sacculations. Peristalsis may occur anywhere in the colon. The movements travel at a lower rate and cover less distance than do the similar movements of the small intestine. They serve to carry ingesta down the colon. They have been studied in carnivores, omnivores, and herbivores by Elliott and Barclay-Smith.

Reverse peristalsis is described as a normal feature of colonic movements in many animals (Elliott and Barclay-Smith; Cannon, 1911; Currie and Henderson). It has been seen in the cat, dog, rat, and guinea pig, and to some extent in the rabbit, hedgehog, and ferret. Alvarez failed to see it in the rabbit, and regards its as of unusual occurrence in man. These reverse waves, traveling over the proximal part of the colon, recur rhythmically about six times a minute and are said, in the rat and guinea pig, to force material into the cecum. Contraction of the cecum then forces the ingesta back into the colon. This to-and-fro movement of the ingesta is continued for a while and disappears when antiperistalsis ceases. In this region of shuttlelike movement of ingesta rapid absorption occurs.

The large intestine of nonruminant herbivores and of omnivores is sacculated, whereas that of carnivores and of ruminants is not. These sacculations are the seat of active contractions, easily and strikingly seen in the rabbit and the guinea pig. They resemble somewhat the pendular movements of the small intestine.

Cecum. The cecum is an organ of small size in carnivores and man, although in herbivores possessing a simple stomach (horse, rabbit, guinea pig) it attains enormous development. The most important function of the cecum of herbivores appears to be that of a reservoir in which cellulose and other food constituents can soak and undergo bacterial fermentation. In harmony with this function, cecal movements are often sluggish. Nevertheless at times they may be powerful. These movements are not of the same type in all animals. In the omnivorous rat alternate contractions of the cecum and antiperistalsis of the proximal colon move the contents back and forth, thus facilitating mixing and absorption. In the herbivorous guinea pig the process is somewhat different. Material passes into the cecum from the ileum distending it; then there occurs a partial emptying of the cecum into the colon by a contraction of the three longitudinal bands of the former. Now antiperistalsis of the colon forces material back into the cecum and this "give and take" between cecum and colon continues for a while (Elliott and Barclay-Smith). In the rabbit cecal contractions are often sluggish and there is little tendency for rhythmic contractions in bits of excised muscle. There is not much co-ordination between the movements of different portions; waves may run simultaneously toward the apex and the base (Alvarez and Starkweather, Alvarez and Zimmermann).

INTESTINAL MOTILITY IN THE HORSE

Observations on intestinal motility in horses have been made by Dukes and Sampson (1936). The animals were anesthetized with chloroform, or were submitted to spinal transection and brain destruction following which artificial respiration was used. The abdomen was then opened and the movements were studied. Moving picture records were made. In the small intestine rhythmic segmentations and pendular movements were common. Their frequency appeared to be less than in small animals. No peristaltic rushes or wavelets were seen. Throughout the large intestine vigorous contractions of the haustra were noted. Propulsion was at times evident in the large intestine.

INTESTINAL MOTILITY IN THE SHEEP AND GOAT

A study of intestinal motility in *sheep* has been made by Dukes and Sampson (1937). The animal to be studied was anesthetized, usually with chloral hydrate, and the abdomen opened. The animal was then transferred to a large tank containing warm physiological saline solution, or the open abdomen was filled with warm paraffin oil. Intestinal motility (as well as motility of the stomach) was studied. Moving picture records were made.

In the small intestine rhythmic segmentations, pendular movements, and peristaltic rushes were seen. At times the rushes followed one another in quick succession. The distance traveled and the speed of the rushes appeared to be less than in the rabbit. Peristaltic wavelets were observed in the upper part of the duodenum. For considerable periods of time the small intestine would be relatively quiet.

The cecum often showed powerful propulsive movements. Reverse waves were also noted. The cecum of ruminants is relatively small and its musculature is powerful. In the sheep it appears to act in large part as a propulsor driving the ingesta through the colon, the spiral part of which seems to offer a good deal of resistance to their passage.

Vigorous motility was commonly seen in the colon. The proximal part, extending from the cecum to the spiral (intermediate) part, showed powerful peristaltic waves and also reverse peristalsis. There was evidence of give and take between the cecum and this part of the colon. The spiral part showed rhythmic swaying movements, a type of motility that looked like rhythmic segmentation, and rushes. The formation of fecal pellets begins in this region. This part is probably active in water absorption, and appears to offer resistance to the passage of ingesta through it.

On the basis of the observations made on the cecum in this study, the view was expressed that the great motor activity and small size of the cecum of the sheep would prevent any considerable amount of bacterial action in it. However, ingesta collected from the cecum and initial part of the colon (considered as a unit) of ruminants, including sheep, show the presence of large amounts of volatile acids (Elsden and co-workers). Evidently, then, fermentation in this part of the large intestine of ruminants is important.

Motility of the large intestine of the *goat* has been studied by Spörri and Asher. A contrast medium was introduced into the large intestine through a cecal cannula and the motility was studied by means of the roentgen ray. The cecum and initial part of the colon showed mainly peristalsis and antiperistalsis. In the spiral part, peristaltic waves and rhythmic segmentations were present. The passage of ingesta in the terminal part of the colon was slow. Pellet formation began in the caudal part of the spiral and was continued into the terminal part of the colon. The contrast medium was observed to pass through the ileocecal valve into the ileum. Water absorption occurred especially in the spiral part of the colon.

These observations indicate that motor activity of the large intestine of the goat is similar to that occurring in the large intestine of the sheep.

INTESTINAL MOTILITY IN THE PIG

Studies of the motility of the stomach (p. 298) and intestine in young swine (3 to 5 months old) have been made by Neimeier. A contrast medium was fed and the movements were studied by means of the roentgen ray. The motor activity of the duodenum is related to that of the stomach. During the first hour after feeding, the duodenum was very active, 5 to 8 boluses a minute passing along. After about an hour there was a period of diminished activity lasting about half an hour. Then greater activity began again. Ingesta quickly reached the jejunum and it filled rapidly, but the progress of ingesta through it was much slower than in the duodenum. One and a quarter to two hours after feeding, the jejunum showed definite motor activity and usually was empty 6 to 10 hours later. Among the movements observed in the jejunum were pendular movements, rhythmic segmentations, a to-and-fro movement of the entire contents of the jejunum, large peristaltic waves that drove the contents before them with great velocity, and smaller peristaltic waves. Motility of the ileum varied in an irregular manner. In some instances the ileocecal sphincter stopped the ingesta, but in others they passed without pause into the colon. Ileal motility diminshed about 5 hours after feeding. In most instances the contents of the ileum entered the cecum, but in some cases the colon received the ingesta first and the cecum was filled next. As a rule the colon received its contents from the cecum. A to-and-fro movement of ingesta between the cecum and colon as occurs in ruminants was believed not to occur in the pig. Cecal motility diminished 6 to 8 hours after feeding. Some 14 to 16 hours after feeding, balls of feces began to leave the colon. They moved along slowly and irregularly, and finally formed a coherent mass of feces.

In roentgen-ray studies of the movements of the colon of the pig, Trautmann and Asher noted pendular, bending, and tonic contractions of the individual portions of the spiral, and peristaltic waves in the colon generally. In the terminal portion of the colon, only peristaltic waves were seen. No antiperistalsis was observed anywhere in the colon.

THE NERVOUS CONTROL OF INTESTINAL MOVEMENTS

The Intrinsic Nervous Mechanism. The movements of the intestine are, like those of the stomach, automatic. That this is true is readily shown by cutting all nerves to the bowel, whereupon the movements continue. The proof may be made more convincing by excising a piece of intestine and placing it in warm oxygenated Locke's solution, whereupon its motor activity continues. As with all automatic muscular organs, so with the intestine, there arises the question whether the impulses for motility are the outcome of activity in the muscle cells of the organ or in the intrinsic nerve cells. The rhythmic movements are, in the light of present knowledge, to be regarded as myogenic. They continue when the intrinsic nerve mechanism of the intestine is paralyzed by nicotine or cocaine (Bayliss and Starling, 1899), and bits of intestine entirely freed of nerve plexuses will beat when suspended in oxygenated Tyrode's solution (Gasser). The rhythmic antiperistaltic movements of the colon are not stopped by nicotine (Elliott and Barclay-Smith) and are therefore probably myogenic. In fact, all muscular rhythm in the stomach, intestine, and elsewhere is probably myogenic in nature (Alvarez, 1928). As regards the true peristaltic movements, these are known to be abolished by nicotine injections or cocaine applications, either of which is believed to paralyze the plexuses in the wall of the gut. From this it appears that peristalsis is dependent on the nervous tissue present in the wall of the bowel. Stomach peristalsis and colonic antiperistalsis, both rhythmic movements, are not dependent on nerve plexuses for their propagation. The excitation seems to travel from muscle cell to muscle cell without the intermediation of a nerve mechanism, for the movements continue after nicotine injection or cocaine application.

The Extrinsic Nerves of the Small Intestine. The musculature of the small intestine receives innervation through the vagi and the splanchnic nerves. The vagi are chiefly motor, stimulation resulting in an increase of tonus and of the rhythmic movements. However, preceding the motor effect there is a brief inhibitory phase. Splanchnic stimulation results mainly in inhibition of movements of the small intestine, though motor effects may be seen. Cannon expressed the belief that the two sets of nerves are in a state of tone. It is probable that the tone is maintained, at least in part, through reflex action. Degenerative section of the vagi and splanchnic nerves does not change the rate of rhythmic contraction in the small intestine of the dog (Douglas and Mann). The vagus nerves to the small intestine appear to be cholinergic (Bunting, Meek, and Maaske). The sympathetic nerves probably are adrenergic.

The Extrinsic Nerves of the Large Intestine. The vagus nerves are believed to have some effect on the proximal part of the colon. However, the principal parasympathetic nerve supply of the large intestine comes from fibers derived from the ventral roots of the second and third sacral nerves. These preganglionic fibers unite, on each side, to form the pelvic nerve (nervus erigens), which is the motor nerve of the large intestine and bladder. The preganglionic fibers terminate around nerve cells located on the bladder and rectum. From these cells postganglionic fibers arise. The large intestine receives also a sympathetic innervation, comparable to that of the small. The nerves are derived from the ventral roots of the lumbar cord and run as preganglionic fibers to the posterior mesenteric ganglia, where they terminate. From nerve cells in these ganglia postganglionic fibers arise to form the hypogastric nerves. These nerves are usually stated to be inhibitory to the large intestine except the internal sphincter of the anus. However, motor responses of the colon to stimulation of its sympathetic nerves have been reported by a number of investigators (Wells and co-workers). The parasympathetic nerves to the musculature of the colon are cholinergic, the sympathetics adrenergic.

Both sets of nerves to the large intestine—the pelvic nerve and the sympathetic—contain afferent fibers. In fact, one-third of the fibers of the pelvic nerve are afferent (Langley and Anderson). Their cells of origin are located in the dorsal root ganglia.

The books by Kuntz, Alvarez, Gaskell, Cannon, and the review of Garry contain full accounts of the innervation of the intestine.

THE RATE OF PASSAGE OF FOOD RESIDUES

The rate of passage of food residues through the alimentary canal has been studied principally by the use of markers such as glass beads or of dyes given with the food or just after feeding. Alvarez and Friedlander (Alvarez, 1928) showed that men to whom beads had been given excreted 70 per cent of the beads in 72 hours, another 10 per cent at the end of 96 hours, and another 4 per cent at the end of 120 hours. Elliott and Barclay-Smith found that rabbits excreted, on the average, 20 per cent of beads in 24 hours, though in some cases they excreted as much as 50 or even 70 per cent in 24 hours. Fish fed Sudan III to men and animals and determined the minimum time necessary for the appearance of the dye in the feces. His results are: man, 15 to 25 hours; cow, 16 to 17 hours; goat, 14 to 17 hours. Using boneblack as an indicator, Guernsey and Evvard found that the average time required for the passage of food residues through the digestive tract of light hogs was 54 hours and of heavy hogs 42 hours.

Ewing and Smith state that feces markers (rubber discs) and color indicators are not practicable means of determining the rate of passage of food residues through steers. By a method based upon a digestion trial and a subsequent slaughter test, they found the average time to be 72 to 84 hours. Most of this time is spent in the rumen. They concluded that fine particles of food pass through the animal more quickly than coarse ones, and that the greater the capacity of the alimentary canal the slower is the passage of food residues.

A review by Lenkeit contains additional data on the rate of passage of food residues in farm animals. See also the review by McAnally and Phillipson (1944).

DEFECATION

Defecation is a complex reflex act whereby the feces are expelled through the anus. The act is usually aided, and may also be inhibited, by the contraction of certain voluntary muscles. From roentgen-ray studies made on man (Hurst) and the cat (Cannon, 1911) during defecation it appears that the whole colon takes part in the act, some of its contents being forced into the rectum. In herbivores it seems certain that colonic activity cannot be so extensive. The emptying of the rectum through the relaxed anal sphincters is now accomplished by the combined contraction of its own wall and of the abdominal muscles. As a result of the contraction of the abdominal muscles with a closed glottis, intra-abdominal pressure (in man) may be raised to as much as 100 to 200 mm. Hg. In man the desire to defecate is associated with the entry of feces into the rectum.

Vigorous horses defecate 5 to 12 times daily; weaker ones more often. Cattle usually defecate more often than horses; dairy cattle defecate 10 to 24 times daily. When fed meat, carnivores defecate only 2 or 3 times daily; when fed mixed food, more often.

Nervous Control of Defecation. Feces in the rectum stimulate sensory nerve endings in the anal region, thus arousing the desire to defecate and starting the chain of reflexes involved. The afferent nerve fibers, in the dog, enter the central nervous system in the dorsal roots of the sacral nerves. Nerve centers controlling the sphincters are found in the lumbosacral cord; and the colon and rectum, although possessing a high degree of automaticity, are probably made to contract more powerfully during defecation by the arrival of impulses from the central nervous system. Nevertheless, defecation may in time take place normally following destruction of the spinal cord, even the sphincters regaining their tone. Hatcher and Weiss found a defecation center in the floor of the fourth ventricle close to the vomiting center. Application of small doses of picrotoxin to this point caused the dogs to defecate.

Chapter XVII

DIGESTION IN THE CHICKEN

THE digestive organs of the chicken are obviously different in several respects from those of mammals. In the chicken teeth are absent, a well-developed crop and gizzard are present, the cecum is double, and a colon is lacking. Such anatomical differences signify differences in the digestive processes. However, the exact nature of the physiological differences is not known in all instances.

The coefficients of digestion of the foodstuffs (Jull), with the exception of cellulose, are about as high in the domestic fowl as in Herbivora.

Scheunert and Krzywanek, and Mangold have reviewed the physiology of digestion in birds. The older review of Brown is an important contribution.

DIGESTION IN THE MOUTH

The method of prehension of food by the chicken is too well known to require description. The beak is the main prehensile structure. Food is retained in the mouth for only a short time.

A complex system of salivary glands is present in the chicken; they are branched tubular glands (Calhoun). The saliva of the hen has been studied by Leasure and Link. The amount secreted by the mature fasting hen in 24 hours varies from 7 to 25 cc., the average being 12 cc. The color of the saliva is milky gray to clear, the odor somewhat putrid. The reaction is nearly always acid, the average being *p*H 6.75. Salivary amylase is always present. A small amount of lipase is also found.

True salivary glands are said to be present in the goose. They are under reflex nervous control and produce a secretion rich in mucin and strongly amylolytic (Nikovlina).

DEGLUTITION

The esophagus of the fowl is wide and dilatable, thus serving to accommodate the bulky, unmasticated food. It terminates in the glandular stomach (proventriculus). Near the thoracic inlet the esophagus widens into the crop. In structure the esophagus of the chicken is similar to that of mammals. The tunica propria contains large mucous glands (Calhoun).

After a brief sojourn in the mouth the food is swallowed. The act of deglutition in birds differs in some respects from that in mammals. Because of the structure of the floor of the mouth, it is impossible for the first phase of swallowing to receive the muscular aid that it does in mammals. The bolus, therefore, instead of being pushed into the pharynx by a contraction of the mylohyoid and other muscles, is propelled backward mainly by raising the head and giving it a quick forward thrust. Thus the inertia of the bolus assists the bird in ingesting it. The esophageal phase of swallowing has been studied in the goose by Cannon and Moser, using the roentgen ray. These investigators found that the food, regardless of its consistency, was carried down the esophagus by peristalsis alone at an average rate of about 1.5 cm. per second. There was no evidence of squirting or shooting of food down the esophagus, as occurs with liquid or semiliquid food in some mammals.

DIGESTION IN THE CROP

The crop in the chicken is well developed. It presents only a few mucous glands, although their secretion is fairly profuse (Browne). According to Shaw, and Schwarz and Teller, no enzymes are secreted in the crop. On the other hand, the work of Hamilton and Card, Hamilton and Mitchell, and Plimmer and Rosedale shows that lactase is present in the wall of the crop and that it is probably concerned in lactose digestion. Whether the enzyme is an endo-enzyme or whether it is actually secreted into the cavity of the crop was not determined. The last-mentioned workers found an amylase in the wall of the crop, but the demonstration of an amylolytic enzyme in extracts of a digestive organ does not prove that the enzyme is of digestive significance. It may be present in the tissue merely because of its presence in blood and lymph.

The crop of the pigeon contains glands which secrete "crop milk." This secretion shows the presence of a large amount of protein and fat. The enzymes amylase and sucrase are present.

The main function of the crop appears to be that of a reservoir for holding, moistening, and macerating the food prior to its passage into the proventriculus. Some bacterial action on food carbohydrates probably occurs in the crop, and digestion of starch by salivary amylase is presumed to take place. The moisture content of crop ingesta is indefinitely variable and seems to show no relation to the kind of food consumed or to the interval after eating (Keith, Card, and Mitchell). No absorption of such simple substances as water, sodium chloride, and glucose occurs in the crop (Schwarz and Teller).

The reaction of the contents of the crop is always acid. The work of Olson and Mann, and Mayhew indicates that the average reaction is approximately pH 5.

The length of time food remains in the crop has been studied by several workers. Steinmetzer withheld food from chickens for 24 hours and, using the roentgen ray, followed the progress of pills composed of oatmeal, barium sulfate, and water through the alimentary canal. The average length of time the food remained in the crop was two hours.

Keith, Card, and Mitchell withheld food from hens and later fed them whole corn, ground corn, or ground corn and a protein concentrate (tankage), and found that whole corn left the crop at the end of 12 to 15 hours; that ground corn left more gradually, a much longer time being required for the crop to empty itself; and that ground corn and tankage left more slowly than whole corn, but more rapidly than ground corn alone.

Heuser studied the rate of passage of ingesta from the crop of the hen. Food was withheld from the birds for a time, after which they were fed. No additional food was given during the experiment. Birds were killed every four hours and the contents of the crop weighed. The results showed that oats were retained in the crop for a longer time than corn or wheat. The rate of passage of food from the crop was influenced by the amount fed. Whole corn remained in the crop longer than cracked corn, and the latter remained longer than corn meal. Wet mash passed from the crop more quickly than dry mash. When grains were fed, the crop contained little or no food at the end of 24 hours.

Movements of the Crop; Hunger Contractions. The crop presents two main kinds of movements, those that have to do with forcing ingesta into the proventriculus and those associated with hunger.

Browne found that if the foods were of the same consistency little or no mixing occurred in the crop. If two foods of equal consistency were fed, they left the crop in the order consumed; but if the foods were of different consistency, the softer food left first.

Patterson (1926-27) studied crop movements in pigeons by making a fistula into the organ, inserting a rubber balloon, and connecting it with a recorder arranged to write on a kymograph. He found that the movements of the filled crop were shallower and less rhythmic than those of the empty viscus.

Observations on crop movements have been made by Ashcraft. Wide variations were found in the type of motility.

The crop is an important seat of *hunger contractions*. A number of observations go to show that hunger returns shortly after eating. Browne expressed the opinion that it returns as soon as there is any accommodation in the crop for food. Patterson, using decerebrate pigeons, found that hunger contractions began 30 to 45 minutes after eating, gradually increasing in frequency and vigor until in 5 or 6 hours they occurred in groups of 6 to 12 or more, separated by intervals of comparative rest of the crop. Rogers, using both normal and decerebrate pigeons in a study of the hunger mechanism, found that restlessness appeared before the crop was completely empty. Lack of water when the crop was filled with dry food caused restlessness. When the crop was well distended with food only occasional contractions could be detected by the balloon method. An hour or two after eating, periodic groups of contractions (hunger contractions) began. These gradually became augmented, and in some birds crop motility was very marked many hours (9 to 14 or more) after eating.

It appears, therefore, that hunger contractions of the crop of birds are comparable to those of the stomach of mammals. The contractions begin, however, when there is relatively more food in the crop of birds than in the stomach of mammals, at least of man and the dog. The proventriculus and gizzard show very active motility during hunger (Ashcraft).

PROVENTRICULUS

The proventriculus is a small, fusiform, glandular organ situated anterior to the gizzard. It communicates with the esophagus anteriorly and with the gizzard posteriorly. The glands of the proventriculus secrete gastric juice. They are described as branched tubular glands. Cells comparable to the parietal cells of mammals are absent from the proventricular glands. A single type of secretory cell is found (Friedman).

The Secretion of Gastric Juice. Gastric juice has been obtained from the chicken by puncture of the gizzard with a small trocar and cannula (Collip). Because of the small size of the proventriculus, its secretion quickly passes into the gizzard. The juice was collected by aspiration with a syringe attached to the cannula. Secretion was stimulated by intramuscular injection of certain tissue extracts or by sham-feeding birds having esophageal fistulas.

Friedman cannulated the proventriculus in acute experiments in pigeons and chickens and made observations on the secretion of gastric juice. The secretion was intermittent. The secretion of acid and of pepsin was found to be controlled by the parasympathetic nerves. Histamine injections caused an increased secretion of hydrochloric acid but not of pepsin. The concentration of pepsin was found to be higher in the gastric juice of the chicken than of the pigeon.

From geese with divided esophagus and gastric fistula Karpov obtained pure gastric juice by sham-feeding.

Keeton, Koch, and Luckhardt showed that in the duck intramuscular injections of "gastrin" cause increased secretion of gastric juice.

Experiments such as these indicate that the gastric juice of birds is similar to that of mammals. Pepsin and hydrochloric acid as present.

The same experiments suggest that the regulation of the secretion of gastric juice in birds is comparable to that in mammals. Cephalic secretion appears to be present in birds. Nervous stimuli via the parasympathetic nerves are effective in exciting the gastric glands. Chemical stimulation is undoubtedly present.

Place of Action of Gastric Juice. Because of the small size of the cavity of the proventriculus food cannot remain long in that location. Therefore the amount of gastric digestion taking place there must be slight. Moreover, Browne points out that the relatively dry nature of the gizzard contents makes it improbable that enzymic action goes on in that organ, all of which points to the duodenum as the probable seat of the main action of gastric juice. This view is strengthened by the fact that the reaction of the duodenum is nearly always acid and that the pancreatic juice and bile enter the duodenum not near its origin but at its posterior extremity.

Movements of the Proventriculus. These have been studied by several workers, among them, Ashcraft, who made kymographic recordings of the motility: "All tracings of the glandular stomach show characteristic form, i.e., a rather slow, moderately high contraction, then more or less incomplete relaxation, followed by a further rise, more rapid and of greater intensity."

GIZZARD (VENTRICULUS)

This peculiar organ is well developed in the chicken. It has no counterpart in the mammal, although it has been compared to the pyloric part of the mammalian stomach. The muscular wall of the gizzard is thick and powerful and the organ is lined with a keratinized layer which is an exudate from the underlying glands (Calhoun). No digestive juice is secreted in the gizzard.

The essential function of the gizzard is to crush and grind the coarse ingesta fed to it by the crop, which acts as a hopper for the gizzard. As already pointed out, the relatively dry nature of the contents of the gizzard makes it improbable that gastric juice exerts much action on the food there. The reaction of the gizzard is, as one would expect, acid (average reaction, *p*H 4.06—Olson and Mann).

Movements. Various types of movement have been recorded. Contractions recur at intervals of 20 to 30 seconds. During hunger the gizzard shows vigorous and continuous motor activity (Ashcraft). Movements of the gizzard and the action of drugs on the movements have been studied by Henry, Macdonald, and Magee. The motor responses of the organ to drugs (atropine, pilocarpine, ergotoxine, adrenaline) were such as to lead to the opinion that the extrinsic nervous control of the gizzard is brought about by the vagus and splanchnic nerves.

The pressure exerted by the contracting gizzard is considerable. It has been measured in the hen, goose, and duck by inserting a balloon into the gizzard by way of the esophagus and connecting the balloon to a mercury manometer. The mean results obtained are: hen, 138 mm. Hg; duck, 178 mm. Hg; goose, 257 mm. Hg (Kato).

Effect of Removal of the Gizzard. Complete surgical removal of the gizzard has been accomplished by Burrows. Gizzardectomized fowls may live in good health indefinitely. The digestibility of coarse foods was much reduced in the gizzardless birds. With ground food the difference in digestibility was much less (Fritz, Burrows, and Titus).

Significance of Grit in the Gizzard. There is a widespread impression that for the gizzard to be an efficient grinder it must contain grit. It is held that the bird, because it possesses no teeth, must have this substance in order to utilize seeds, grain, and other compact, resistant foods. However, in recent years considerable evidence has accumulated that seems to show that grit is not essential for the well-being of the chicken. Bethke and Kennard could find no evidence that grit was injurious, yet they could find none that it was beneficial even in the case of chicks reared to maturity. A group of birds that never received grit remained healthy and grew to maturity, utilizing their food, including whole corn and wheat, apparently just as well as those that had free access to grit. Bethke and Kennard concluded, however, that in the case of mineral deficiency in the food grit might serve as a source of mineral.

Buckner, Martin, and Peter studied the question of the importance of grit for growing chickens and obtained similar results. Their findings led them to conclude that grit is not essential to growth and egg production in White Leghorn chickens up to 8 months of age.

Fritz found that feeding grit to birds slightly improved the digestibility of various foods. The effect of grit was most evident when coarse food was used.

Titus expressed the following views on the feeding of grit: "Although grit is not absolutely essential, it permits chickens to make more efficient use of whole grains and of coarse, fibrous feeding stuffs. Apparently, grit also tends to prevent gizzard erosion in chicks when finely ground feed that contains little fiber is fed."

Kaupp and Ivey made a study of the length of time grit remained in the gizzard of mature hens following its complete withdrawal from the food. The fowls, 25 in number, were killed or died from causes not related to the question of grit in the gizzard, over a period of a year, and the contents of the gizzard were examined for grit. In no instance was it absent. Even hens that were kept as long as 300 days or more showed the presence of considerable quantities. While these findings show that the gizzard holds tenaciously to a quantity of grit when none is fed to the chicken even over long periods of time, they do not show that the grit retained serves a useful purpose in the gizzard.

DIGESTION IN THE INTESTINE

The small intestine extends from the gizzard to the origin of the ceca. It is comparatively long and is of nearly uniform size throughout. The large intestine consists of the ceca and the rectum. The ceca, two tubes with blind extremities, originate at the junction of the small intestine and rectum and extend orad toward the liver. The terminal part of a cecum is a good deal larger than the initial part. The intestine throughout its entire course presents villi and simple tubular intestinal glands. Duodenal (Brunner's) glands are not present in the chicken (Calhoun) or turkey (Rosenberg).

Duodenum. The duodenum extends from the stomach (gizzard) to the place of entrance of the bile and pancreatic ducts. The reaction of its contents is nearly always acid (Olson and Mann) and it is probable that gastric juice exerts the greater part of its action here. As previously stated, gastric juice of birds is similar in composition to that of mammals.

Pancreatic Digestion. The action of pancreatic juice of the fowl has not been extensively studied. From such work as has been done, it appears that enzymes similar to those formed by the mammalian pancreas are produced by the avian organ. Thus the old work of Langerdorff shows that the pancreas of the pigeon produces a slightly alkaline, watery juice containing amylolytic, proteolytic, and lipolytic enzymes. The more recent work of Shaw indicates that the pancreas of the chick produces similar enzymes. Shaw states that pancreatic function in the chick is imperfectly developed before the seventh day after hatching. Plimmer and Rosedale have shown the presence of similar enzymes in the pancreas of more mature chickens.

Intestinal Juice and Enzymes. The digestive action of intestinal juice or of extracts of intestinal mucous membrane of birds seems to have been little studied. According to Popow and Kudrjawzew, the intestinal juice of the hen differs only slightly from that of the dog. Hamilton and Mitchell and Plimmer and Rosedale have shown that lactase is not produced in the intestine. Protease, invertase, and amylase are present in extracts of mucous membrane obtained from the intestine as a whole. Amylase is present in cecal extracts, but protease and invertase are absent (Plimmer and Rosedale).

Bile. The digestive action of bile appears likewise to have been studied very little. It is probable that its significance is similar to that of mammalian bile. The *p*H of the bile of the chicken is 6.0 to 6.2 (Buckner and co-workers).

Reaction in the Intestine. A number of studies have been made of the reaction of the alimentary tract of the common fowl (Mayhew; Olson and Mann; Heller and Penquite; Buckner and co-workers; and others). The results obtained by Olson and Mann on the intestine are given in the table.

*p*H OF THE INTESTINE OF THE CHICKEN

Part of Intestine	*p*H		
	Mean	Low	High
Duodenum	6.31	5.64	7.10
Jejunum	7.04	6.12	8.01
Ileum	7.59	6.93	8.42
Right cecum	7.08	5.83	8.20
Left cecum	7.12	5.93	8.16
Rectum	7.38	6.29	8.18
Coprodeum	7.24	5.69	8.10

Farner has studied the *p*H of various portions of the digestive tracts of chickens, pigeons, ducks, pheasants, and turkeys.

Ceca. An extensive study of the physiology of the ceca of the chicken has been made by Browne. This worker performed experiments on healthy chickens in which he fed them solid food (dough) stained with methylene blue or magenta, or drenched them with methylene blue solution, or injected methylene blue or magenta solution through the cloaca. At various intervals afterward, the birds were killed and the contents of the intestine and ceca examined. Some of his more important conclusions are as follows: (1) The usual cecal content consists of chocolate-colored, pultaceous material. (2) The proportion of ingesta entering the ceca varies directly with the fluidity of the contents of the large intestine (rectum). (3) A considerable part of the intestinal content does not enter the ceca; only fluids enter. (4) Fluids given by mouth reach the blind ends of the ceca in one and a half to four hours, depending upon the quantity administered. (5) Fluid injected into the cloaca reaches the blind ends of the ceca almost immediately.

Browne regards the ceca as playing an unimportant part in digestion, for even in certain grain-eating birds they are absent. In his opinion they are mainly for absorptive purposes. On the other hand, the work of Radeff and others suggests that they are concerned in the digestion of cellulose, thus tending to bring their function into line with that of the ceca of Herbivora. Radeff found that hens could not digest the crude fiber of barley at all, but digested the crude fiber of wheat grains to the extent of 5 per cent; of oats, 7 per cent; and of crushed corn kernels, 17 per cent. After removal of the ceca the crude fiber of wheat grains was digested only to the extent of 1.4 per cent and of crushed corn in general not at all.

Olson and Mann made extensive observations on the physiology of the ceca of the chicken and reviewed the literature. Dyes added to dry food could be found in the cecum 24 to 48 hours after being fed. Lampblack, mixed with the food, failed to enter the cecum in significant amounts even when fed for a long period. The dyes carmine and rose bengal left the ceca 120 hours after the last feeding of the dyes. Olson and Mann did not detect the very rapid passage (one and a half to four hours) of material into the ceca as reported by Browne.

Effect of Removal of the Ceca. That the ceca of fowls are not essential structures is indicated by the fact that they can be removed or occluded without evident ill effect on the bird (Richardson; Durant; Hunter, Durant, and Hogan; Schlotthauer and co-workers). Surgical occlusion of the ceca in turkeys protects the birds against the infection of blackhead (Durant; Schlotthauer and co-workers). However, the method has not come into practical use.

RATE OF PASSAGE OF INGESTA

This question has been studied by a number of workers using different methods. Browne found that the minimum time required for oats (as indicated by their husks) to appear in the feces when fed to chickens was about five hours, while an entire meal of oats passed through the digestive tract in 18 to 20 hours. Browne found that food dyes were unsatisfactory for determining the rate of passage of ingesta.

Steinmetzer, using the roentgen ray, followed the progress of pills composed of oatmeal, barium sulfate, and water given to chickens fasted for 24 hours before the experiment. The time required for the food to pass through the gastro-intestinal canal was four hours.

Kaupp and Ivey used lampblack as an indicator in the food and found that the average time required for the indicator to appear in the feces was for the growing fowl, 3 hours and 52 minutes; for the laying hen, 3 hours and 46 minutes; for the adult hen not in laying condition, 8 hours; for the broody hen, 11 hours and 44 minutes.

Using the roentgen ray, Henry, Macdonald, and Magee showed that the alimentary canal of the fowl empties itself in 16 to 26 hours after the ingestion of food.

Chapter XVIII

ABSORPTION

ABSORPTION is the process whereby foods, properly prepared by the organs of digestion, are transferred from the lumen of the gut to the blood or lymph. By means of the blood the absorbed foodstuffs are transported to the tissues for utilization or for storage.

THE PLACE OF ABSORPTION

No food absorption takes place in the mouth and esophagus. Strychnine may be absorbed from the pharynx (Meltzer), and strychnine and picrotoxin are said to be rapidly absorbed from the mouth. In the stomach,[1] contrary to what might be supposed, absorption is very limited under normal conditions. On the whole, the food substances are not yet ready for absorption: proteins are not split below the peptone stage, fats are hydrolyzed only to a slight extent, and carbohydrate digestion is, in most animals, far from complete. As regards water, it is doubtful whether it remains in the stomach long enough to undergo any significant reduction in volume. There is little reason to believe that inorganic salts are ordinarily absorbed from the stomach in significant amounts. Certain drugs may be absorbed from the stomach of some animals. Meltzer states that Bouley and Colin obtained rapid effects of strychnine introduced into the stomach of the dog, pig, and cat with ligated or paralyzed pylori. In the cow the effect was retarded, and in the horse it was absent or at least not fatal. Meltzer showed that strychnine is not absorbed from the stomach of the rabbit, whereas hydrogen cyanide is.

The small intestine is the chief seat of absorption in carnivores and omnivores and is doubtless of great importance as an organ of absorption in herbivores a swell.

The large intestine as an organ of absorption is of limited importance in carnivores and man, except in the initial part of the colon where water absorption occurs. The large intestine of all herbivores, on the contrary, must be well adapted for absorption. This would seem to be especially true in the simple-stomached herbivores, where such extensive digestive changes are reserved for the large bowel. It is probably less true of ruminants, where stomach digestion and absorption are so important. In the intestine, digestion and absorption proceed side by side.

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[1] For a discussion of absorption from the ruminant stomach, see p. 338.

ABSORPTIVE SURFACES

The mucous membrane of the small intestine is highly modified as an organ of absorption by the presence of numerous tiny fingerlike projections known as villi. These vary considerably in form and length in the different animals, being, according to Ellenberger, longest in carnivores, shorter in solipeds, and shortest in swine and ruminants. In general, animals with the most rapid digestive and absorptive processes have the best-developed system of villi.

A villus is composed of a projecting core of tunica propria covered with the columnar epithelial lining of the intestine. Near the axis of the villus is found a large lymph capillary known as a lacteal. It begins near the tip of the villus and enters a plexus of lymph vessels lying just on the inner side of the muscularis mucosae. At their origin the lacteals are often branched. The villus possesses also a rich network of blood capillaries, and many lymphocytes are found in the meshes of its reticular stroma. Smooth muscle fibers derived from the muscularis mucosae enter the villus, to whose basement membrane many are attached. The motor activity of the muscularis mucosae, including the muscle strands of the villi, has been studied by King and Arnold, who found that the mucosa as a whole shows ridging, pitting, and grooving movements, while the villi show shortening, lengthening, and lateral movements, singly and in groups. The movements of the villi and of the mucosa may or may not be associated. The movements are believed to be myogenic. They are probably related to mixing, absorption, lymph flow, and the expulsion of mucus from the goblet cells. The muscularis mucosae has been further studied by King and Robinson, who paid particular attention to the nervous mechanisms regulating it. They suggest that the muscularis mucosae may have functions not connected with absorption and secretion. It may be concerned with transport of ingesta in the gastro-intestinal canal.

Investigations by Kokas and Ludány indicate that the movements of the villi are augmented by a hormone present in the mucosa of the duodenum and activated by hydrochloric acid. The name *villikinin* is given to the hormone. It is not the same as secretin, cholecystokinin, histamine, or choline.

The mucous membrane of the large intestine is devoid of villi, but in herbivores it must be well adapted to absorb.

In the domestic animals the size of the absorbing surface, exclusive of the villi, has been estimated to be as follows (Sussdorf, cited by Gmelin): horse, 12; ox, 17.1; pig, 2.8; dog, 0.52; cat, 0.129 square meters. The extent to which the villi increase the absorbing surface varies in different animals, depending upon the size and number of the villi. In man it is estimated that the increase is 7- to 18-fold.

ROUTES FOR ABSORBED FOODSTUFFS

There are two routes by which absorbed foodstuffs may enter the general circulation: the lymph and the blood of the portal system.

Lymph Route. The lymph capillaries of the mucous membrane of the intestine, including the lacteals of the villi, drain into the larger lymph vessels of the submucosa. These penetrate the muscular coat of the bowel and empty into the lacteal vessels of the mesentery, which have intimate connections with the mesenteric lymph nodes. The lacteal vessels of the mesentery proceed to the cysterna chyli into which they empty. The latter vessel is continued forward as the thoracic duct, which empties into the venous system anterior to the heart. Fats are absorbed principally by the lymph.

Blood Route. The blood capillaries of the mucous membrane of the intestine, including those of the villi, unite to form venules and veins, which drain into the portal vein via its mesenteric radicles. The portal vein enters the liver, where its blood is mixed with that of the hepatic artery. The hepatic veins convey the blood of the liver to the posterior vena cava. Protein and carbohydrate digestion products, water, and inorganic salts[1] are absorbed largely by the blood.

THE MECHANISM OF ABSORPTION

Much interest has centered around the question as to how the foodstuffs in the intestine are conveyed to the blood or lymph. It may be said that theories of absorption fall into three general groups. (1) Absorption is an act explainable in terms of recognized physical or physicochemical processes such as osmosis, diffusion, imbibition, and intraintestinal pressure. (2) Absorption is a process dependent upon special activity of the epithelial cells lining the intestine and is at present unexplainable in physicochemical terms. (3) Absorption takes place in accordance with special activity of the epithelial cells together with certain physicochemical activities such as osmosis, diffusion, etc. The evidence for and against these and other views of absorption was reviewed by Goldschmidt, who reached the conclusion that while factors other than osmotic may be active in modifying the process of absorption, all the evidence points to their physicochemical nature. In the light of more recent evidence, this conclusion probably requires amplification. It is held that absorption is due *in part* to some special property of the epithelial cells (Magee, 1930). These structures expend energy in absorption, at least in certain phases of the process. Ingraham and Visscher have suggested a mechanism to account for active absorption from intestine.

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[1] The absorption of the inorganic salts is discussed in Chapter XXVI.

The mechanism of absorption from the alimentary canal is a part of the broad problem of cell permeability and thus falls to a large extent in the realm of general physiology.

No nerves whose specific function is to control absorption from the intestine have been found. The intestinal vasomotor nerves, however, by virtue of their control of the blood supply, must have some influence on absorption.

FAT ABSORPTION

Fats undergo hydrolysis in the intestine to fatty acids and glycerol. In this form they are absorbed. Fats themselves are insoluble in water, but fatty acids formed from their hydrolysis are water-soluble in the presence of bile. The bile salts enter into chemical combination with the fatty acids, thus increasing their solubility. Bile is necessary for normal fat absorption. In the absence of this secretion, much of the fat appears in the feces, not in the form of neutral fat, but of fatty acids, which indicates that the disturbance is not one of splitting but of absorpion.

The fatty acids and the glycerol penetrate the free ends of the epithelial cells of the intestinal lining and enter their interior. Histological studies of fat absorption reveal the presence of numerous fat droplets in the cytoplasm of the epithelial cells, and it is generally believed that the droplets arise by a synthesis of the fatty acids and glycerol to neutral fat. As the fat globules approach the basal ends of the cells, the globules decrease in size. They now enter the tissue spaces of the tunica propria and pass from there to the lymph capillaries of the villi. The lymph current then removes them to the mesenteric lymphatics and the thoracic duct, which enters the venous system anterior to the heart. The finely divided, absorbed fat is in the form of an emulsion and imparts a milky appearance to the lymph, which during fat absorption is termed chyle. The amount of fat in chyle during absorption may be as much as 3 or 4 per cent. The fat particles (chylomicrons), 0.5 to 1 micron in diameter, can be seen, and have been studied, by the aid of the dark-field microscope (Gage and Fish).

Recent work shows that during fat absorption there is an active phospholipid metabolism in the mucous membrane of the intestine. The fatty acids of the phospholipids of the mucosa change with changes in the fatty acids of the food. These findings have been interpreted as indicating that phospholipids play an intermediary role in the synthesis of fatty acids to neutral fat. Their fatty acids are believed to be displaced by fatty acids derived from the food. Later they yield these fatty acids to the lymph and receive others from the alimentary canal. The fatty acids appear in the lymph as neutral fat. Some of the phospholipid itself undergoes absorption into the lymph. While it is generally agreed that phospholipids are formed in the cells of the intestinal mucosa, some workers regard the phospholipids as end-products and not intermediate compounds in the resynthesis of fats.

During fat absorption leucocytes accumulate in the mucous membrane, and their significance in the transfer of fat from the epithelial cells to the lymph system has been much debated. Modern work indicates that they are not important in fat absorption.

Since ample facilities are present in the bowel for fat hydrolysis, there can be little doubt that fat is absorbed in a hydrolyzed form. Some authorities believe that it is absorbed practically entirely in this form (Verzár and McDougall; Bloor, 1939). However, present evidence indicates the possibility of the absorption of some unhydrolyzed fat in the form of a fine emulsion, the particle size averaging less than 0.5 micron in diameter (Frazer). According to this view of fat absorption, the glyceride fraction of fat in the intestine, that is, the unhydrolyzed fraction, is absorbed mainly via the lymphatics, whereas the fatty acid fraction is absorbed mainly by the portal circulation. This concept of fat absorption has been designated as the *partition hypothesis*. The postulate that complete hydrolysis of fat occurs prior to absorption is designated as the *lipolytic hypothesis*. The former probably offers a better explanation of the old observation that not more than 60 per cent of the absorbed fat could be recovered from a fistula of the thoracic duct. The possibility exists, of course, that the remaining 40 per cent of the fat entered the blood by lymph channels other than the thoracic duct, but it seems more probable in the light of recent work that it entered the portal vein after hydrolysis to fatty acids in the intestine.

In the dog, nevertheless, the recent work of Freeman makes it evident that lymphatic paths from the intestine to the blood, in addition to the thoracic duct, do exist.

Evidence has been presented by Conrad and Scott that fatty acid absorption in the hen takes place to a very large extent by way of the portal system.

A study of fat absorption in swine, with particular reference to the lipids of the duodenal mucosa, has been made by Reiser.

The absorption of *cholesterol* apparently requires the presence of bile salts as well as the simultaneous absorption of fat. A good deal of cholesterol is converted into esters during absorption. Cholesterol is absorbed principally by the lymph.

PROTEIN ABSORPTION

Ample facilities in the form of enzymes (pepsin, trypsin, peptidases) are provided for protein digestion. The principal end-products of this digestion are amino acids. However, some of the hydrolysis of protein apparently does not go beyond the peptide stage. In the form of amino acids and peptides, therefore, proteins are absorbed. The portal blood is the route of their absorption. Significant absorption of amino acids by the lymph is not believed to occur.

In the blood stream amino acids can be detected by several methods, one of the most interesting of which is that of Abel, Rowntree, and Turner, in which the blood of the living animal is submitted to vividiffusion by being passed through a series of collodion tubes connected with an artery and a vein of the animal and immersed in saline solution. The solution surrounding the collodion tubes may be drawn off periodically and its constituents recovered. By this method it can be shown that amino acids are always present in blood, and that their concentration increases following the ingestion of protein or following the introduction of amino acids into the intestine.

For a discussion of the absorption of globulins after colostrum ingestion in the newborn, see p. 50.

CARBOHYDRATE ABSORPTION

The digestion of carbohydrates by enzymes results in the formation of monosaccharides, whereas the digestion by bacteria results in the formation of simple fatty acids such as acetic, propionic, and butyric. The monosaccharides are absorbed, for the most part, into the portal blood and are carried to the liver, although the lymph stream has been shown to remove some sugar from the alimentary canal. The lower fatty acids are absorbed by the blood.

Lower fatty acids have been found in significant amounts in the blood draining the cecum of the sheep, the cecum and colon of the pig, the colon of the horse, and the cecum of the rabbit. The blood draining the small intestine did not contain significant amounts of the lower fatty acids in any species studied (sheep, pig, horse, rabbit) except apparently the pig (Barcroft, McAnally, and Phillipson, 1944b). For the absorption of the lower fatty acids from the ruminant stomach, see p. 333.

Although maltose, sucrose, and lactose are dialyzable substances, they are not absorbed as such except when consumed in very large amounts, and even then the extent of their absorption is slight. Disaccharides do not enter the blood stream because of the existence of their corresponding disaccharidases in the wall of the intestine. These enzymes insure the conversion of the disaccharides to monosaccharides during absorption. When for any reason disaccharides do get into the blood stream, either by absorption or by parenteral introduction, they are largely eliminated unchanged in the urine, although it appears that maltose, at least, when introduced into the body in either way, is utilized to some extent, probably because of the existence of a blood enzyme that hydrolyzes it to glucose.

The work of Cori shows that the rate of absorption of different sugars from the intestine is not the same. Representing the rate of absorption of glucose as 100, the rate of absorption of galactose is 110; fructose, 43; xylose, 15; arabinose, 9; lactose, 30. The rate of absorption of glucose and other monosaccharides is fairly constant regardless of the amount of sugar ingested. The latter factor determines the duration of absorption but not the rate.

Absorption of glucose from the intestine of the chick has been investigated by the Cori technic designed for studies on rats (Golden and Long). An absorption rate of 400 mg. per 100 gm. of body weight per hour was found. The rate remained practically constant over a 4-hour period and did not appear to be influenced by differences in concentration of the glucose solutions administered (30 to 40 per cent). The absorption rate obtained in chicks is more than twice that found in rats of similar size and over four times that found in dogs.

The monosaccharides in the portal blood reach the liver, where to a considerable extent they are stored in the form of glycogen. Other tissues, notably the skeletal muscles, also have the power to form and store glycogen (p. 485).

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PART V

The Kidneys and Urine; The Skin

Chapter XIX

THE SECRETION AND DISCHARGE OF URINE

THE KIDNEY secretes urine. One of the principal organs of elimination, it aids in keeping the composition of blood plasma constant by (1) the excretion of nitrogenous waste products such as urea, (2) the elimination of inorganic salts, (3) the elimination of water, and (4) the removal of nonvolatile, soluble foreign substances that may have gained entrance to the blood. In accordance with the kidney's function, changes in the composition of blood plasma bring about corresponding changes in kidney activity and in the composition of the urine. The kidney is thus of great importance in the maintenance of the constancy of the internal environment of the organism; in short, it is one of the chief homeostatic mechanisms of the body.

HISTOLOGY OF THE KIDNEY

The kidney is a gland without embryological or histological analogy elsewhere in the body. The kidney is made up of many units termed nephrons, each of which begins as a peculiar structure known as the glomerular capsule and runs as a tubule, the renal tubule, through the cortex and medulla to empty with many similar nephrons into a collecting duct. These ducts empty into the pelvis or the calyces of the kidney.

The glomerular capsule may be regarded as a sphere of flattened epithelial cells invaginated at a pole by a tuft of capillaries known as the glomerulus. This tuft of vessels is therefore surrounded by two layers of epithelium, which are separated by a narrow space. The inner layer is closely applied to the capillaries. A capsule and a tuft of vessels together constitute a renal corpuscle (Fig. 99). The capsule is connected to the tubule by a neck. This part is succeeded by a very tortuous proximal convoluted portion, which is continued downward toward the pelvis of the kidney as the thin segment of the medullary loop. This is followed by the thick segment of the medullary loop and then the distal convoluted portion, which empties, by way of the initial collecting tubule, into the terminal collecting duct. The initial collecting tubule represents the termination of the nephron.

The structure of the epithelial cells in the different parts of the nephron is not the same. These structural differences suggest differences in function, and as between the capsule and the tubule, functional differences are generally recognized. As to the specific function of the different parts of the tubule, less is known. However, knowledge in this field is increasing, and the topic will be referred to later.

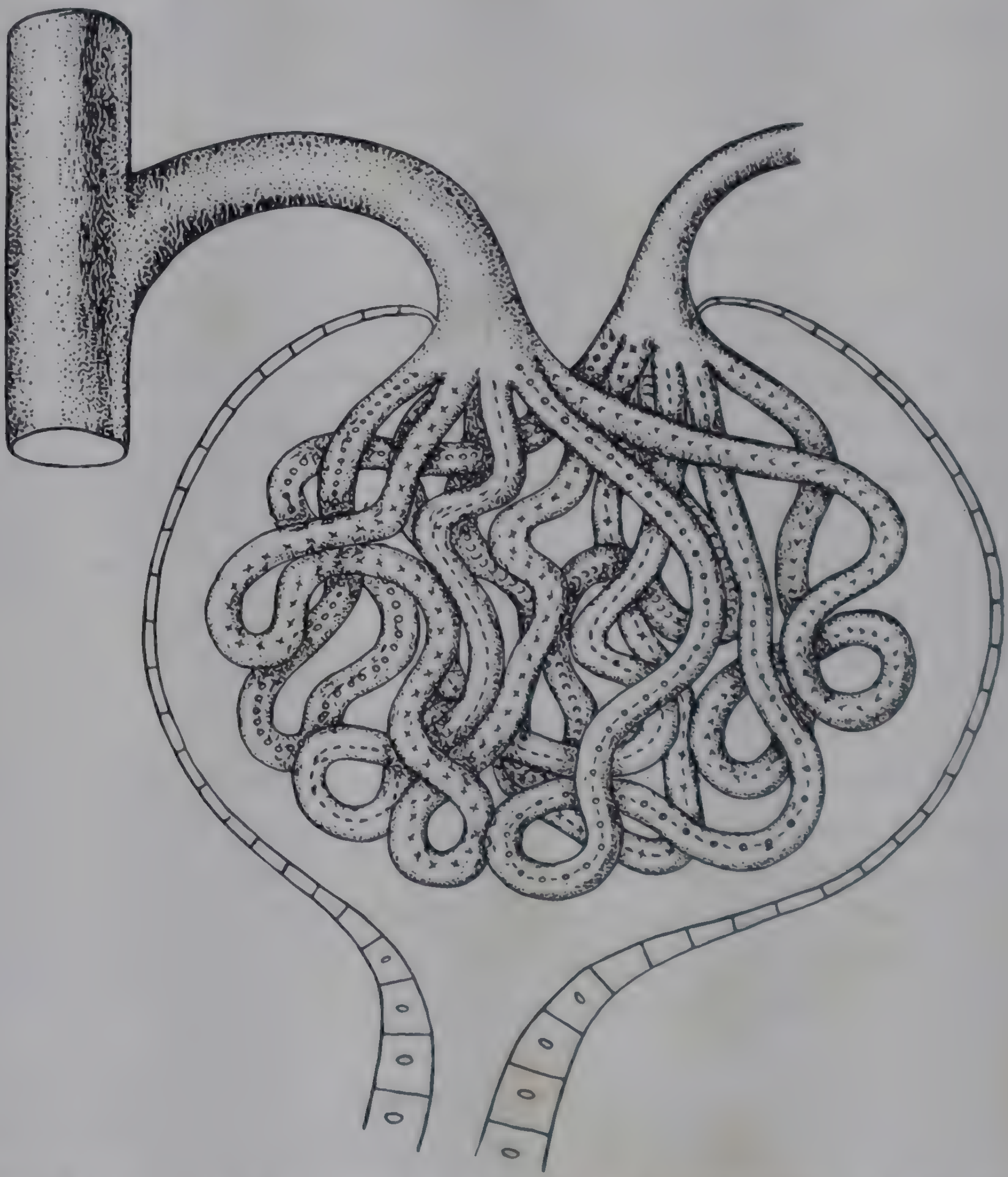


Fig. 99.—Diagram of a glomerulus, showing the arrangement of the capillary loops. Note the twisted loops and the absence of anastomoses. (From Vimtrup, *American Journal of Anatomy,* 1928, **41.**)

Renal tubules isolated from the kidneys of adult rabbits have a length of 2 to 3 cm. The diameter of the renal corpuscle of mammals varies between 100 and almost 200 microns (Huber).

Using an improved method, Kunkel made observations on the number and size of glomeruli in the kidneys of several mammals. He found that the number and size of glomeruli, and therefore the total glomerular capillary surface, were more closely related to body surface area than to any other measurement. Among the different species studied it was found that the number of glomeruli, in both kidneys, per square meter of body surface varied from 1,300,000 to 3,100,000. The following figures show some of the actual counts (one kidney): 410-kg. ox, 3,992,000; 43-kg. pig, 1,248,000; 50-kg. pig, 1,138,000; 13 dogs ranging in weight from 3.29 to 20 kg., 318,000 to 726,000; 2.75-kg. cat, 184,000; 3.5-kg. cat, 214,500.

The Effect of Loss of Renal Sustance. There is a large factor of safety in the amount of renal substance. About two-thirds may be removed without causing serious disturbances to the animal. The blood urea concentration rises temporarily following the resection; the blood pressure is normal. Hypertrophy of the remaining renal substance occurs, but there is no evidence of the new formation of nephrons (Allen, Bollman, and Mann).

When one kidney is removed the blood flow through the other kidney increases and reaches a maximum in about a month. Experiments indicate that the increase is 50 per cent or more.

BLOOD SUPPLY

The blood supply of the kidney is derived from the renal artery, which, upon entering the organ, divides and redivides in a rather definite manner until certain interlobular or radiate branches are formed. From these vessels afferent glomerular vessels leave in groups of two, three, four, or even more (Huber), to pass directly to a renal corpuscle. Upon entering the corpuscle the afferent vessel breaks up into numerous capillaries constituting the glomerulus. The capillaries of the glomerulus do not anastomose. They reunite to form the efferent glomerular vessel, which is of smaller caliber than the afferent vessel. Immediately after the efferent vessel leaves the renal corpuscle, it breaks up into a second capillary network around the adjacent tubules. All blood reaching the capillaries of the different parts of the tubule, both in the cortex and the medulla, must first pass through the capillaries of the glomerulus. This view, though not universally recognized, is well supported by the work of Huber, MacCallum, and others. The two capillary networks are in series with each other. The small size of the efferent arteriole helps to insure a high pressure in the glomerular tuft and provides for a low pressure in the peritubular capillary net. These facts have a bearing on the theory of renal function, as will be seen later. The blood from the second set of capillaries is drained to the renal vein. The oxygen content of the blood in the renal vein is higher than that in most veins. Evidently the blood supply of the kidney in relation to its oxygen needs is quite adequate.

Both the afferent and the efferent arterioles of the glomerulus are provided with peculiar myo-epithelioid cells. Between the afferent and efferent vessels there is a group of cells, possibly neural or secretory, well supplied with nerve fibers. These cells and the myo-epithelioid cells constitute a juxta-glomerular apparatus probably concerned in the regulation of the tonus of the afferent and efferent arterioles and thus the blood pressure and flow through the glomeruli. The juxta-glomerular apparatus is present in all the common mammals (Smith, 1939; Loitey). While much remains to be learned about the functioning of the juxta-glomerular apparatus, there is good evidence that the circulation through the glomerular tuft of capillaries is influenced by changes in the afferent glomerular arteriole as well as the efferent.

Of timely interest in connection with the glomerular functions are certain studies on the glomerular circulation. By illuminating the ex-posed kidney of the frog by reflected light, Richards and Schmidt dem-onstrated that the number of glomeruli showing active circulation varie widely in different preparations and was not maximal. The numbe could be increased by many agents, including salt solution, urea, glu-cose, and caffeine, and could be decreased by adrenaline or pituitrin The number of open capillaries in a given glomerulus was similarly variable. Blood flow often shifted from glomerulus to glomerulus.

The question of glomerular intermittence has been studied i mammals by the indirect method of injecting substances into the bloo stream and examining the glomeruli for injected material afterward The work of Hayman and Starr and of Khanolkar supported the ide of glomerular intermittence in mammals, but in the more recent ex-periments of White the evidence indicated that under normal condi-tions all the glomeruli of the mammalian kidney are open all the tim The question of glomerular intermittence in mammals requires furthe study.

NERVE SUPPLY

The nerve supply of the kidney is derived from the splanchnic an vagus nerves, mainly through the celiac ganglion, where most of th synaptic junctions are located. The splanchnic fibers leave the spina cord in the ventral roots, chiefly of the sixth to the thirteenth thoraci nerves. They supply vasoconstrictor and vasodilator fibers to the kid-neys, the former kind predominating. The function of the vagus fiber has not been determined (Gruber).

The question of the existence of secretory nerves to the kidney is an old and important one. The balance of evidence favors the view that such nerves are not present and that the control exercised by the renal nerves over the secretion of urine is due to vasomotor effects (Cushny; Marshall, 1926; Gruber). Strong evidence against the view that the kidney is provided with secretory nerves of importance is furnished by experiments in which a kidney when removed and then transplanted to some other part of the body or reimplanted in the same location functions apparently normally. In fact, a single reimplanted kidney is able to maintain the life of the animal for an indefinite time (Gruber). Obviously, transplanted or reimplanted kidneys are completely removed from nervous control, at least for a time.

METHODS OF STUDYING RENAL FUNCTION

These may be said to fall under three general heads. (1) Acute experiments on anesthetized operated animals or on isolated organs have been widely used. This method permits experimental simplification by the control of many variables, but the question arises as to what extent the results can be applied to the normal animal. (2) By determining the relative concentration of various substances in blood and urine it is possible to calculate the concentration undergone by the substance during elimination and, if the rate of urine formation is known, to calculate the amount of filtrate produced by the glomeruli in a given time. To make the latter calculation valid it is necessary to use a substance that is readily filtered by the glomeruli and neither secreted nor absorbed by the tubules. Of the normal blood constituents, creatinine seems to be the best for use in the determination of such ratios, or renal clearances. Of the foreign substances that have been injected into the blood in studies of this kind, inulin, a nontoxic polysaccharide, is thought to give the most satisfactory results. (3) Studies, both structural and functional, in the comparative field are useful. Here nature herself has made experiments on the kidney, particularly on the renal tubule, during the evolutionary process.

THE MECHANISM OF RENAL SECRETION

Until 1917 the two principal theories of urine secretion were the Bowman-Heidenhain and Ludwig theories. According to the first of these, the cells of the glomerular capsule secrete water and salts such as sodium chloride, while the epithelium of the tubule secretes most of the solids of the urine such as urea and uric acid. In short, according to this theory, urine is formed by specific secretory activity of certain cells of the nephron, much as saliva is formed by the cells of a salivary gland.

According to Ludwig's theory the glomerular capsule is a simple filter allowing all plasma constituents except proteins to pass through; and in the tubule this dilute lymphlike filtrate is made into urine by the return of water to the blood by diffusion. This is a physical theory.

In 1917 Cushny enunciated a "modern" theory of urine secretion which may be stated briefly as follows: Blood as it passes through the glomerular capillaries is subjected to a process of filtration, whereby water and the dialyzable plasma constituents are forced into the space between the layers of the glomerular capsule. The filtrate, lymphlike in character, is protein-free because the glomerular membrane is impermeable to the blood proteins. During its passage along the renal tubules, the filtrate is concentrated by a process of selective absorption. As a result substances that are of further use to the organism are returned to the blood, whereas substances of no value to the organism and any excessive amounts of useful substances are rejected. The liquid containing the rejected substances is urine. The reabsorbed liquid is of invariable composition and closely resembles Locke's solution.

According to this theory, therefore, the glomeruli are filters and the tubules selective absorbers. In the latter respect, chiefly, it differs from Ludwig's theory, according to which absorption in the tubules is governed by diffusion pressure.

Recent researches have confirmed Cushny's views with respect to glomerular filtration and selective absorption in the tubules. The idea that the absorbed liquid is of invariable composition has not received support. It is now known that differential absorption occurs in the renal tubule. Cushny's theory did not include the elimination of substances by the cells of the tubules. More recent work has shown that both tubular excretion and tubular synthesis are factors in the formation of urine. These activities will be discussed later.

The beat of the heart determines the height of the general blood pressure and this in turn the height of the glomerular pressure, which, minus the opposing osmotic pressure of the blood colloids and the intracapsular pressure, is the filtration force. Direct measurement of the blood pressure in the capillaries of the glomeruli of mammals has not been accomplished, but the ureteral or intrapelvic pressure necessary to stop urine formation can readily be measured by cannulating the ureter or the pelvis of the kidney and connecting the cannula to a vertical glass tube. The urine rises in the tube until its hydrostatic pressure equals the secretion (filtration) pressure. The intrapelvic pressure required to stop the secretion of urine averages, in unanesthetized dogs, 78 mm. Hg (McDonald, Mann, and Priestley). The wide range of pressures is shown in Fig. 100.

In the dynamic state, when the urine outflow from the kidney is unobstructed, an intracapsular pressure must be taken into account. In dogs this has been estimated to equal some 10 to 20 mm. Hg. This pressure opposes the filtration pressure and must be subtracted from it to give the *effective filtration pressure:* 78−15=63 mm. Hg. Granted an average effective filtration pressure of 63 mm. Hg, there is little difficulty in understanding the adequacy of filtration at the glomerulus.

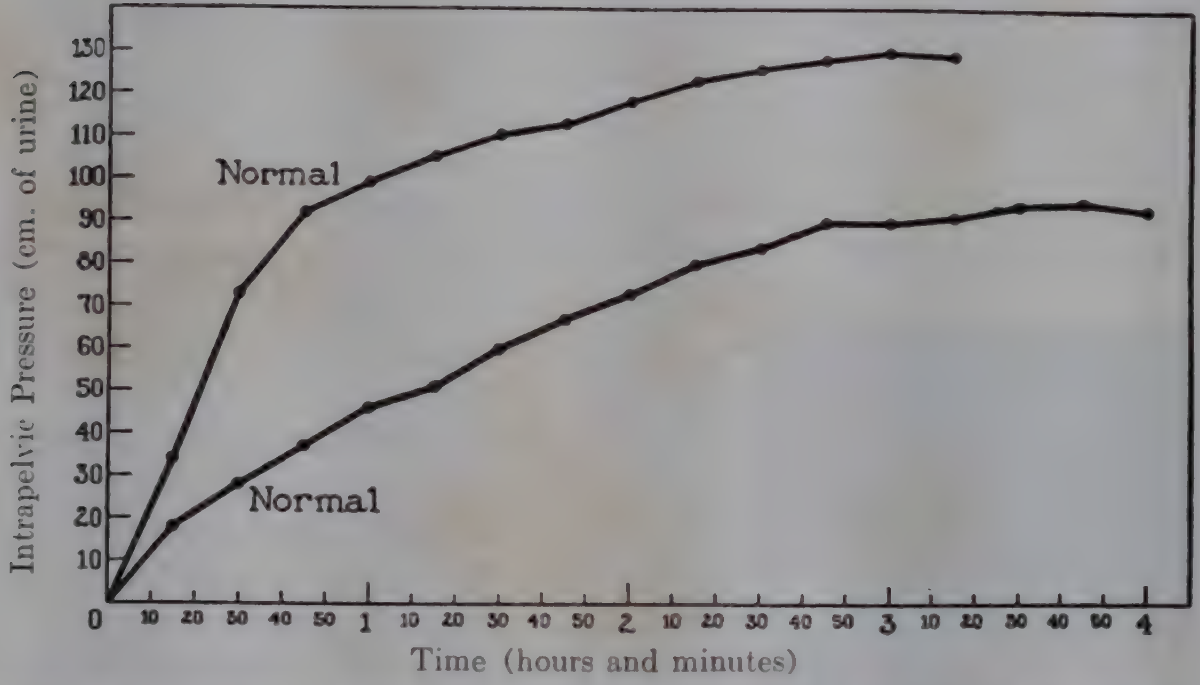


FIG. 100.—Intrapelvic pressure (secretion pressure of the kidney) of two dogs, to show the wide range of pressures encountered in normal dogs. (From McDonald, Mann, and Priestley, *Journal of Urology*, 1937, 37.)

The osmotic pressure of the blood proteins is about 22 mm. Hg. This pressure added to that necessary to stop urine formation ought to give a rough estimate of the capillary pressure: 78+22=100 mm. Hg. Capillary pressures of this magnitude do not occur elsewhere in the body, so far as is known. The anatomical arrangement of the renal circulation and other considerations suggest that pressures of this size can actually be present in the glomerular capillaries.

The epithelial cells of the tubule supply the energy for reabsorption, which must be of considerable magnitude when it is considered that the osmotic pressure of urine is normally several times greater than that of blood. This means that the tubule cells have to expend much energy in concentrating the copious glomerular filtrate.

Evidence for Filtration. Certain lines of evidence indicating that the glomerular membrane acts passively and as a filter in the process of urine formation may be summarized as follows: (1) The anatomical arrangement is such as to suggest filtration. (2) Liquid obtained directly from the glomerular capsule of the frog by puncture with a capillary pipette contains sodium chloride and sugar, whereas urine obtained simultaneously from the bladder contains neither (Wearn and Richards). This is direct evidence of absorption in the tubules and may be regarded as indirect evidence of glomerular filtration: if the glomeruli were not blind filters but were selective eliminators (secretory mechanisms) it would be unnecessary for tubular absorption to occur; only excretory products would pass through the glomeruli. Because the glomeruli are blind filters, however, valuable constituents escape into the tubules, and reabsorption must occur. (3) In several species of lower vertebrates it has been shown by Richards and his co-workers that the concentration of solutes in the fluid obtained by glomerular puncture (glomerular urine) is the same as in the blood plasma of the animals. For the frog this has been shown to be true of chloride, uric acid, phosphate, reducing substances, and creatinine; for Necturus, chloride, reducing substances, and phosphate; for the snake, uric acid. Furthermore, it has been shown by determinations of the *p*H that glomerular urine and blood plasma, in both frogs and Necturi, have the same reaction. These findings may be regarded as proof that the glomerulus in these species behaves in a nonselective (passive) manner and has the function of a filter. (4) Changes in the pressure in the renal circulation when the blood flow through the organ is kept constant result in parallel changes in the rate

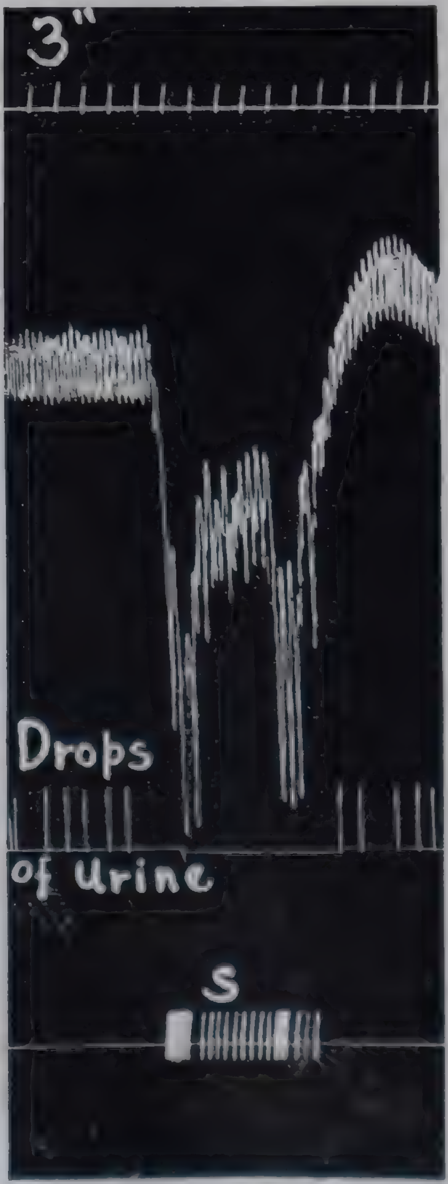


FIG. 101.—Tracing showing the relation between general arterial blood pressure and urine formation. When the blood pressure fell, owing to stimulation of the peripheral end of a vagus nerve (*s*), the flow of urine stopped. The urine flow was recorded in drops from a ureter. The blood flow was uncontrolled.

of urine formation (Richards and Plant). This strongly suggests that the passage of liquid across the glomerular membrane is due to a physical force (filtration) and not to secretory activity, which would not run parallel with the blood pressure. (5) When the action of the tubules is stopped by poisons added to the blood or by asphyxia, a liquid similar in composition to protein-free plasma is obtained from the ureter. It is probable that this liquid is a glomerular filtrate. (6) Under certain conditions the amount of urine formed may be increased without any increase in the oxygen consumption of the kidney (Hayman and Schmidt). This tends to show that the increased flow under these conditions is due to physical and not secretory activity, for the latter would necessitate an increase in the metabolism of the gland.

Changes in the systemic blood pressure in relation to urine secretion are shown in Fig. 101. In evaluating this tracing it should be kept in mind that blood flow was an uncontrolled factor.

Evidence for Reabsorption. There is much evidence—some direct, some indirect—that reabsorption takes place in the tubules (Marshall, 1926; Cushny; Walker and co-workers). Very strong evidence is that brought forward by Wearn and Richards, mentioned above. They obtained liquid from the glomerular capsule of the frog's kidney in amount sufficient for analysis. Such liquid contained chloride and under some conditions glucose, whereas bladder urine collected simultaneously contained neither. This is convincing evidence of reabsorption, at least of chloride and glucose. That water is also absorbed is indicated by experiments, already mentioned, in which when tubular action was suppressed a very dilute urine was secreted. That energy for reabsorption is supplied by the epithelial cells of the tubules and not by diffusion pressure alone, that is, that a mechanistic view of reabsorption is incorrect, is indicated by the fact that some of the substances in the urine may be many times more concentrated than in the blood. Clearly, such a concentration could not be effected by diffusion. Nor is the degree of concentration the same for all solutes. Sulfates are concentrated about 90 times; creatinine, 75 times; urea, 60; phosphate, 16; potassium, 7; chloride, 2; etc. The oxygen consumption of the kidney in diuresis may be several times that during rest. According to present conceptions, the increase in metabolic rate is brought about by increased activity of the cells of the tubules.

The Place of Reabsorption. That selective reabsorption occurs in the tubules of the kidney is now generally accepted. Much progress has been made in Richards' laboratory in determining the parts of the tubule where absorption occurs and the nature of the substances absorbed. Richards and Walker have devised technics whereby fluid, in amounts adequate for analysis, can be obtained from different known places in the renal tubules of amphibia, and whereby definite parts of the lumen of an individual tubule can be perfused with different solutions. Using these technics, Walker and co-workers have shown that chloride is reabsorbed in the distal convoluted tubule; that glucose reabsorption takes place in the proximal convoluted tubule; that phlorhizin (p. 463) prevents the active reabsorption of glucose by the proximal convoluted tubule; that about one-third of water reabsorption occurs in the proximal tubule and two-thirds in the distal tubule; that the acidification of urine in the tubule of Necturus is brought about by the distal segment of the tubule; that the proximal tubules can actively absorb phosphate.

To what extent these results apply to mammals is unknown, but it seems reasonable to assume that they have significance for all kidneys.

The Rates of Filtration, Reabsorption, and Blood Flow. The magnitude of the filtration and reabsorption processes in the normal kidney in the formation of urine may be illustrated by the following figures for man. The rate of glomerular filtration, as determined in inulin clearance studies, is about 125 cc. per minute, or 170 liters for a 24-hour period. The amount of urine produced in 24 hours is about 1.5 liters. These figures show that 99 per cent of the water filtered by the glomeruli is reabsorbed by the renal tubules. It is evident that a large blood flow through the kidney is necessary to produce this volume of filtrate. Renal clearance studies made with diodrast (a synthetic, iodine-containing organic substance) indicate a blood flow for the kidneys of man of about 1800 liters daily. Thus it is seen that the blood loses some 10 per cent of its water as filtrate in passing through the glomeruli. This loss results in a corresponding increase in the osmotic pressure of the plasma proteins, which of course are not filtered. There is believed to be a low capillary pressure in the peritubular capillary net. Reabsorption from the tubules would therefore be facilitated by the higher osmotic pressure of the plasma proteins and the low hydrostatic pressure in the capillaries. However, most of the energy for reabsorption is derived from metabolic activity of the cells of the tubules.

Secretion as a Factor in Urine Formation. According to Cushny's theory, true secretion has little or nothing to do with urine formation. However, more recently a good deal of evidence has accumulated which seems to show that secretion must be taken definitely into account when the function of the tubules is being considered. Ammonia, hippuric acid, and perhaps other substances are believed to be formed in the tubule cells and secreted, while certain foreign substances such as phenol red are probably concentrated in the tubule cells and then secreted. Morphological and experimental studies on the kidneys of lower vertebrates are proving helpful in attempts to solve the question of secretion in the tubules (Marshall, 1934). Studies on the toadfish indicate that the renal tubule of this creature can secrete. Since the tubule in this animal is composed only of the proximal convoluted segment, it follows that this part can be secretory. The proximal convoluted segment is found throughout the vertebrate phylum; it is unlikely that it has entirely lost its secretory function. It is therefore probable that some secretory activity of this part of the renal tubule occurs in all kidneys. Secretion in the mammalian kidney is believed to be more primitive and less important than filtration and selective reabsorption. Tubular excretion (secretion) is the subject of a review by Shannon.

THE EXCRETION OF WATER BY THE KIDNEY

Water reabsorption occurs in the convoluted portions of the renal tubules, particularly in the distal convoluted segment. The ability of the tubule cells to reabsorb water depends on the presence of an *antidiuretic hormone* produced by the posterior lobe of the pituitary gland and a hormone, or hormonal influence, diuretic in action, produced by the anterior lobe of the pituitary. The antidiuretic hormone is closely related to the pressor principle of the posterior lobe.

Removal of the posterior lobe of the pituitary, or injury to the supraoptic nucleus of the hypothalamus or to the tract that runs from this nucleus to the posterior lobe, provided that at least a part of the anterior lobe is present, results in *diabetes insipidus*. This condition is characterized by the elimination of great quantities of urine (polyuria) and by intense thirst. This combination of circumstances—absence of the antidiuretic hormone and presence of the diuretic hormone, or hormonal influence, of the anterior lobe—reduces the ability of the renal tubules to absorb water and polyuria results. The urine in this condition is very dilute. The polyuria of diabetes insipidus can be relieved by injection of extracts of the posterior lobe of the pituitary. The supraoptic nucleus and its tract to the posterior lobe control the secretion of the antidiuretic hormone.

The diuresis which follows the ingestion of water probably involves this pituitary-renal mechanism. The slight increase in the water content or decrease in the electrolyte content of the plasma may be the factor that suppresses the production of the antidiuretic hormone by the supraoptico-hypophyseal mechanism and thus leads to water diuresis. In dehydration the production of the antidiuretic hormone is stimulated and water absorption by the kidney is increased. The secretion of the antidiuretic hormone has been reviewed by Pickford.

Desoxycorticosterone of the adrenal cortex promotes the absorption of sodium by the kidney tubule and thus has an indirect effect on water elimination.

THE RENAL REGULATION OF ACID-BASE BALANCE

The food of carnivores and man has an excess of potential acid-forming substances (sulfur and phosphorus) over the intake of available base. When this potential acid is liberated in the oxidative processes in the body, it is neutralized by base given up by the bicarbonate of the body fluids. If the acid were excreted from the body combined with this base, there would soon be a severe decrease in the alkali reserve of the body and acidosis would result. There are two renal mechanisms whereby this acid can be excreted without a loss of an equivalent amount of fixed base from the body.

In the first place, the slightly alkaline glomerular filtrate presented to the tubules is converted into a liquid which contains acid in free form. This means a saving of base to the organism. The process whereby the renal tubules convert an alkaline glomerular filtrate into an acid urine has been reinvestigated by Pitts and Alexander. The underlying principle appears to be the addition of hydrogen ions to, and the taking up of sodium ions from, the glomerular filtrate as it passes along the tubules. The source of the hydrogen ions is the tubule cells, probably those of the distal convoluted portion. Apparently the hydrogen ions are derived from carbonic acid in the cells, this being formed from carbon dioxide and water under the influence of the enzyme carbonic anhydrase (p. 225). The Na^+ taken up by the cells in exchange for H^+ is removed by the blood as sodium bicarbonate.

In the second place, fixed base is conserved by the kidney by the formation of ammonia in the tubule cells and the conversion of some of the sodium salts in the glomerular filtrate into ammonium salts which are excreted. The nitrogen-containing precursor from which the ammonia is formed is brought to the kidney by the blood, and various views have been held as to its chemical identity. Recent work indicates that glutamine is the most important source of the ammonia formed in the kidney. Amino acids may be a source of a small amount of the ammonia (Peters and Van Slyke).

The food of herbivores contains an excess of potential base, principally in the form of potassium salts of various organic acids. When these substances are oxidized in the body, bicarbonates are formed. The excess is removed from the blood by the kidney and contributes to the alkalinity of the urine.

THE CONTROL OF RENAL SECRETION

The kidney is well supplied with nerves, but, as has been stated, these are believed by most workers to be mainly vasomotor in function and not secretory. It is therefore necessary to seek along other lines the explanation of the regulation of the amount of urine secreted. It is evident that the following factors may influence the volume of urine formed: the rate of glomerular filtration, the rate of tubular reabsorption, or a combination of the two.

The rate of glomerular filtration may be varied by changes in glomerular blood pressure and blood flow, changes in the size of the filtering surface (in amphibia, at any rate—p. 402), and changes in the colloid content of the blood plasma.

The rate of tubular reabsorption is influenced by the rate of passage of the glomerular filtrate along the tubules, the osmotic pressure of the fluid in the tubules, the osmotic pressure of the colloids and the hydrostatic pressure of the blood in the capillaries of the tubules, and the activity of the tubule cells. Hormones and other chemical factors are important regulators of the activity of the tubule epithelium. Apparently the renal nerve supply does not affect the activity of the renal tubules (Rustum Maluf).

THE PASSAGE OF URINE FROM THE KIDNEY TO THE BLADDER

Urine, secreted continuously though at a varying rate, passes through the collecting ducts into the pelvis or the calyces of the kidney, whence it is conveyed to the urinary bladder by the ureter. The pelvis of the kidney is the funnellike beginning of the ureter. The latter is a tubular structure whose wall contains a good deal of smooth muscle. This muscle is capable of peristaltic contraction, which doubtless is the main factor concerned in the propulsion of urine along the tube into the bladder. Pendular movements and antiperistaltic activity may also be present. Lucas found that under normal conditions the pressure in the relaxed ureter is practically zero, the amount of urine necessary to cause peristalsis being extremely small. The ureter is innervated by the autonomic nervous system. It appears that inhibitory fibers are supplied by the sympathetic and motor fibers by both the sympathetic and the parasympathetic (Gruber).

THE FILLING AND EMPTYING OF THE BLADDER

The ureter pierces the wall of the bladder at such an acute angle that a highly competent ureterovesicular valve is formed. It effectively prevents reflux of urine under any condition of pressure that may be present in the bladder. The urinary bladder, like other hollow muscular organs, possesses, within limits, the power of accommodating itself to increases in its contents without any material increase in the internal pressure. Therefore as urine enters the bladder its walls become distended, outflow of urine into the urethra being prevented by the tonic contraction of a sphincteric mechanism at the neck of the bladder. However, when the pressure in the bladder reaches about 150 mm. of water (man), contractions of its walls begin, relaxation of the sphincters occurs, and reflex urination, or micturition, takes place. Ordinarily the emptying of the bladder is assisted by contraction of the abdominal muscles, but this assistance is not necessary. The musculature of the bladder wall, although visceral, can be made to contract more vigorously by cortical reinforcement of the spinal centers of micturition. The urination reflex not only may be assisted by voluntary effort, but, as is well known, it may be opposed voluntarily within wide limits. This is accomplished by inhibition of the spinal centers of micturition and by contraction of the external sphincter, which surrounds the upper part of the urethra. The desire to urinate arises from the stimulation of receptors in the wall of the bladder by stretch and contraction of the musculature.

The Nervous Control of the Bladder. The bladder is supplied by nerves derived from the sympathetic and parasympathetic divisions of the autonomic nervous system. The preganglionic sympathetic fibers leave the spinal cord in the second to the fourth lumbar nerves and run to the posterior mesenteric ganglion, where most of them terminate synaptically. From this ganglion postganglionic fibers reach the bladder through the hypogastric nerves. The parasympathetic fibers run as preganglionic fibers in the pelvic nerves (nervi erigentes) and make synaptic junction with nerve cells situated diffusely over the surface of the bladder. From these cells short postganglionic fibers pass to the musculature of the organ. Both sets of nerves contain afferent fibers. That the action of these nerves varies in animals of different species is clearly indicated by the work of Elliott, who studied the condition in the dog, cat, rabbit, goat, pig, and other animals. (See also the review of Gruber.)

In all mammals the pelvic (parasympathetic) nerves cause contraction of the whole bladder, and there is general agreement that they are its main motor nerves. In the cat and rabbit, and perhaps other animals, they also are inhibitory to the internal sphincter. Hence these nerves may be regarded as the nerves of urination.

In the cat the hypogastric (sympathetic) nerves cause contraction of the urethra and relaxation of the bladder. They thus facilitate the holding of urine. In the pig the situation appears to be similar to that in the cat but less marked. In the dog hypogastric nerve control is limited to a small area near the sphincter, which contracts when the nerve is stimulated. In the rabbit and female goat the situation is similar to that in the dog, but in the male goat the contraction tends to involve the whole bladder. According to Gruber the hypogastric nerves carry both motor and inhibitory fibers to the bladder.

The external sphincter of the bladder is under the control of somatic nerves.

There are several nerve centers in the spinal cord that are concerned in the micturition reflexes, but the volitional act of micturition is integrated at higher levels of the central nervous system, namely, the hypothalamic area and the cerebral cortex. Following transection of the spinal cord, the spinal reflexes of micturition are disturbed, but after a time co-ordinated action of the centers returns.

Chapter XX

THE URINE

PHYSICAL AND PHYSICOCHEMICAL PROPERTIES OF URINE

URINE is essentially a solution of the products of nitrogen and sulfur metabolism, of inorganic salts, and of pigments. It is usually yellowish in color; however, wide normal variations may occur. The normal color is due mainly to the pigment urochrome. The odor is characteristic for the different species. In most animals the consistency is watery; but in the horse it is thickish and more or less syrupy, owing to the secretion of the mucous glands in the pelvis of the kidney and the upper part of the ureter. In most animals the urine is clear when voided; in the horse it is turbid, chiefly by reason of suspended crystals of calcium carbonate, which settle out upon standing. The urine of ruminants becomes turbid upon standing because of the precipitation of the same salt.

Specific Gravity. The specific gravity of urine varies with the relative proportion of dissolved matter and water. In general, the greater the volume, the lower is the specific gravity. Specific gravities for domestic animals and man (Ellenberger and Scheunert) are shown in table.

SPECIFIC GRAVITY OF URINE

Species	Range	Mean
Horse	1.025–1.060	1.040
Ox	1.030–1.045	1.032
Sheep and goat	1.015–1.045	1.030
Pig	1.010–1.050	1.012
Dog	1.016–1.060	1.025
Cat	1.020–1.040	1.030
Man	1.010–1.030	1.020

Molecular Concentration. The depression of the freezing point is a measure of the molecular concentration of a solution. The following freezing-point values for urine from different species have been obtained: horse, –1.77 to –2 degrees C.; dog, –1.573 to –3.638 degrees C.; cat, –5 degrees C. (Ellenberger and Scheunert). It is evident that in all cases the molecular concentration of urine is much higher than that of blood plasma (averaging freezing point = −0.59 degrees C.). This means that the kidney does work in the secretion of urine.

Reaction. The reaction of the urine varies in different species and from time to time, in individual animals, depending on the food and the metabolism. As with all solutions, so with urine, the reaction is determined by the relative concentration of H and OH ions. When the former predominate the urine is acid, when the latter predominate it is alkaline. The ratio of the concentration of hydrogen ions to hydroxyl ions in the urine is governed largely by the character of the food but partly by metabolism. Carnivorous animals generally have an acid urine, herbivorous animals an alkaline urine, and ominvorous animals a urine that is either acid or alkaline depending upon the diet. Most foods of animal origin give rise to an acid urine because they contain an excess of acid-forming elements (sulfur, phosphorus, chlorine), whereas many foods of vegetable origin give rise to an alkaline urine because they contain an excess of base-forming elements (sodium, potassium, calcium, magnesium). Thus when the sulfur and phosphorus of protein (of the food or of the tissues) are oxidized in metabolism, sulfuric and phosphoric acids result. These are neutralized by base derived from the bicarbonate of the body fluids and are excreted in the urine—the former as a neutral salt, the latter as Na_2HPO_4 and NaH_2PO_4. In the urine of carnivores and man the monobasic salt is usually in excess, and when it is the urine is acid. For the way in which the kidney converts the alkaline glomerular filtrate, in which there is an excess of the dibasic salt, into acid urine, see p. 410.

The vegetable foods contain large amounts of such salts as acid potassium malate, citrate, acetate, and tartrate, which when oxidized in the body yield bicarbonates, principally of sodium and potassium. These salts, to the extent that they are present in the body fluids beyond the needs of the organism, are eliminated in the urine and tend to give it an alkaline reaction. Cereals, having a fairly high protein content, behave like foods of animal origin in that they tend to give rise to an acid urine. In herbivores hippuric acid, formed in the body by the conjugation of benzoic acid and glycine, tends to make the urine acid, but there is usually enough alkali present completely to convert the acid into a hippurate.

As with biological fluids generally, the reaction of urine is best expressed in terms of the hydrogen ion concentration, and is usually written as a *p*H value (see Chapter I). Ashworth and Brody report the *p*H range of the urine of dairy cattle as 7.4 to 8.4. Most of the values were

8.0 or over. A similar range has been found by Metzger. In 40 sheep Healy, Bullard, and Spears found the urine to be acid only twice; in all other cases it was alkaline. In normal human subjects the *p*H of the urine varies from 4.8 to 7.4. The average is about 6.

It has been shown in cattle that an excess of basic over acid constituents in the diet is unnecessary for well-being; animals can grow normally to maturity when the usual alkalinity of the urine is shifted to the acid side. It is suggested that the acid-base ratio in dietaries is important only when the excess of one over the other is so great that the liberal mechanisms for the preservation of the normal reaction of the tissues are strained (Theiler, Green, and Du Toit). Mineral acids (hydrochloric, sulfuric, phosphoric) are used to preserve silage. The question arises as to the effect of these acids on the acid-base balance of animals fed the silages. Investigations indicate the desirability of supplementing these silages with either basic salts or with roughages containing a good surplus of base (Lepard and co-workers). The organic acids of silage present no special problem, since they are in general readily oxidized.

Amount. The amount of urine secreted daily varies with the food, work, external temperature, water consumption, season, and other factors. Marked pathological variations may occur. The figures in the table illustrate the daily amounts in the domestic animals.

DAILY AMOUNT OF URINE

Animal	Range	Average	Author
	liters	*liters*	
Horse	2–11	4.7	F. Smith
Dairy cow	8.8–22.6 kg.	14.2 kg.	Fuller
Sheep and goat	0.5– 2	1	Ellenberger and Scheunert
Pig	2– 6	4	Ellenberger and Scheunert
Large dog	0.5– 2	1	Ellenberger and Scheunert
Man	1– 1.2		Hawk

CHEMICAL COMPOSITION OF URINE

The chemical composition of urine is extremely complex. This is not surprising when one considers that it is formed directly from the blood in order that the composition of the latter may be kept constant. The following are the principal normal constituents of urine: water, urea, creatinine, purines (uric acid, xanthine, hypoxanthine, etc.), allantoin, hippuric acid, ammonia, amino acids, ethereal sulfates, neutral sulfur compounds, inorganic salts, and the pigments urochrome and urobilin. In addition, foreign and pathological substances may be present.

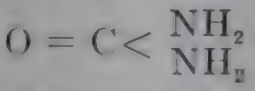
Nitrogenous Constituents. Small amounts of nitrogenous wastes occur in sweat, saliva, and milk, but the urine is by far the principal medium for their elimination. The chief ones are urea, creatinine, uric acid or allantoin, purine basses, hippuric acid, ammonia, and amino acids.

The following figures (Hunter 1914-15) may be taken as illustrative of the percentage distribution of nitrogen in the urine of *fasting* sheep:

Urea	79.8 –84.0
Ammonia N	2.5 – 3.2
Creatinine N	3.9 – 4.2
Creatine N	1.8 – 3.9
Uric acid N	0.26– 0.73
Purine base N	0.38– 0.66
Allantoin N	1.7 – 2.3
Undetermined N	4.2 – 5.9

In a *nonfasting* cow the percentage distribution of nitrogen was found to be as floows (Hart and co-workers):

Urea N	74.07
Creatinine N	6.07
Creatine N	6.01
Hippuric acid N	4.19
Allantoin N	3.68
Uric acid N	0.59
Ammonia N	0.48
Purine base N	0.056

Urea. In mammalian urine, urea is the most important of the nitrogenous waste products. The generally accepted formula for this compound is  $O = C<\begin{matrix}NH_2\\NH_2\end{matrix}$ which is carbamide. Urea occurs not only in urine but is present in practically all tissues and fluids of the body.

That the nitrogen of mammalian urine is present largely as urea nitrogen is indicated by figures already given for the sheep and the cow, and by the following additional figures which show the percentage of total nitrogen that exists as urea nitrogen, according to various authors (Fearon): dog, 86.2; rabbit, 82.8; cow, 58.1 to 69.4; sheep, 81.9 to 84.5; goat, 70.0 to 79.2; man, 87.5 per cent. The percentage of urea itself in the urine of certain mammals is as follows: dairy cow, 1.5 to 3.5 per cent (Hayden); sheep, 0.32 to 5.53 per cent, average 2.54 per cent (Healy, Bullard, and Spears); man, 1.9 to 2.5 per cent (Fearon).

Urea is formed mainly, though not directly, from protein. Some urea arises from derivatives of tissue proteins (endogenous source) and some from derivatives of food proteins (exogenous source). Under ordinary conditions much the greater part of the urea found in the urine is of food origin. However from recent experiments in which isotopic nitrogen and deuterium were used to mark the amino acids, it is evident that the distinction between the metabolism of the tissue proteins and that of the food proteins is not as clear-cut as was formerly thought. The new work shows that there exists a dynamic equilibrium between the amino acids of the tissues and those of the internal environment not revealed by previous work (p. 460).

The immediate precursors of urea are amino acids and ammonium salts. The mechanism of urea formation in the animal body is not completely understood. Amino acids, which normally represent the principal source of urea, must first undergo deamination by which the amino group is split off, probably as ammonia. This is then converted to urea. A recent theory of urea formation, the Krebs-Henseleit theory, is that ammonia and carbon dioxide unite with the amino acid ornithine ($NH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHNH_2 \cdot COOH$) to form citrulline ($NH_2 \cdot CONH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHNH_2 \cdot COOH$) which then unites with more ammonia to form arginine ($NH_2 \cdot CNHNH \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHNH_2 \cdot COOH$). This is hydrolyzed by the enzyme arginase to ornithine and urea. The ornithine may be used over and over again in the production of urea. It acts as a catalyst. Arginase is found in the liver of mammals but not of birds. This accounts for the failure of birds to form urea. The formation of urea is considered also in Chapter XXIII.

The place of urea formation has been studied particularly in the dog. In this animal the liver appears to be the sole place (Bollman, Mann, and Magath, 1924), as is indicated by the disappearance of urea from the blood when the liver is removed. It is now held, on the basis of additional work involving several species and including in vitro studies of liver slices, that the liver is the sole seat of urea formation in the mammalian body (Snyder). The conversion of arginine to ornithine and urea by the liver enzyme arginase is the reaction that is limited to the liver. The other reactions can occur in other tissues.

Ammonia. In man ammonia stands next to urea in importance as an end-product of protein metabolism. It constitutes 2.5 to 4.5 per cent of the total urinary nitrogen. In herbivorous animals, however, it is not normally so important. Thus in cattle ammonia nitrogen represents only 0.101 to 0.272 per cent of the nitrogen of the urine and in horses only 0.071 to 0.096 per cent (Beccari). Ammonia occurs in the urine normally as the chloride, phosphate, or sulfate. Such salts as ammonium carbonate, carbamate, and lactate, to the extent that they are formed in the body, are converted to urea. The kidney is the source of the urinary ammonia and its significance in the normal regulation of acid-base balance, particularly in carnivores and man, is considered elsewhere (p. 410).

When fat metabolism is abnormally accelerated, the ketone substances—acetoacetic acid, β-hydroxybutyric acid, and acetone—are formed in increased amounts. Two of these, β-hydroxybutyric and acetoacetic acids, to the extent that they are not oxidized or otherwise disposed of in the metabolic processes, require neutralization, and for this purpose they draw upon the fixed base of the body. In this form they are carried to the kidney, where they are removed in the glomerular filtrate. In the kidney, ammonia is formed and is substituted for the fixed base in combination with the acids, which then appear in the urine as ammonium salts. The fixed base is conserved by the body.

Fasting, diabetes in man and the dog, and ketosis in ruminants are instances in which fat metabolism is accelerated and the ketone substances are produced in increased amounts.

Creatine. This substance, methyl-guanidoacetic acid, $C_4H_9O_2N_3$, is found in the skeletal muscles of every class of vertebrate, in the heart muscle of mammals, in the urine of birds, under special conditions in the urine of mammals, and elsewhere. During growth and pregnancy and in the puerperium, creatine is normally found in the urine. This probably applies to mammals generally. At other times, when there is no creatine in the diet, the urine of normal mammals contains little or no creatine.

An earlier view that creatine is a waste product of tissue metabolism cannot be accepted at the present time. Creatine occurs more abundantly in skeletal muscle than in any other tissue, and the rapidly contracting pale muscles contain more than the slowly contracting red ones. These observations, the finding that much of the creatine of muscle is combined with phosphoric acid, and other facts make it evident that creatine plays an important part in muscle contraction and metabolism (p. 563).

Recent evidence (Schoenheimer and Ratner) indicates that creatine is derived in the body as follows: The union of glycine and a fraction of arginine (amidine) yields guanidoacetic acid. This undergoes methylation to form creatine, the methyl group being derived from methionine or choline. The principal sites of creatine synthesis are the liver and kidney. The formation of creatine in the chicken is believed to involve the same mechanism as in the mammal.

Creatinine. This substance, the anhydride of creatine, is never absent from the urine of mammals, and this is where it occurs chiefly (Hunter, 1928). It is found in low concentration in blood. Hunter states that Munzer found the following average amounts of creatinine in the urine of mammals: ox, 1.12; horse, 1.94; sheep, 1.44; goat, 0.38; pig, 1.49 gm. per liter. The *creatinine coefficient* is the number of milligrams of creatinine nitrogen eliminated daily per kilogram of body weight. In man the normal range of the coefficient is approximately 7 to 11. Closely similar figures apply to animals; in cattle Ashworth and Brody found the coefficient to be 9.5. It has been shown that creatinine excretion tends to increase directly (linearly) with the body weight in mature animals of many species (Brody, Proctor, and Ashworth). This is in contrast with basal metabolism, endogenous (minimum) nitrogen excretion, and neutral sulfur elimination, all of which tend to increase with the 0.73 power of body weight. Brody makes the following statement: "The direct proportionality between creatinine [excretion] and body weight is in conformity with all the evidence that creatinine represents the muscular mass of the body." The creatinine excretion is an index of the metabolic activity of the tissues, especially skeletal muscle.

As regards the origin of creatinine, recent work confirms a widely held view that it is derived from creatine. An isotope of nitrogen was used in obtaining an unequivocal answer (Schoenheimer and Ratner).

The Purines and Allantoin. The principal purine found in the urine of man is uric acid ($C_5H_4N_4O_3$). Smaller amounts of other purines, the purine bases, are also found. These are adenine ($C_5H_3N_4NH_2$), guanine ($C_5H_3N_4ONH_2$), hypoxanthine ($C_5H_4N_4O$), and xanthine ($C_5H_4N_4O_2$). In the urine of mammals generally, except man and the chimpanzee, uric acid occupies a minor position; it is largely replaced by its oxidation product allantoin ($C_4H_6N_4O_3$). The accompanying table (Hunter and Givens) shows the percentage distribution of allantoin nitrogen and purine nitrogen in the urine of a number of animals and man.

PERCENTAGE DISTRIBUTION OF ALLANTOIN N AND PURINE N IN URINE

Species	Allantoin N	Uric Acid N	Purine Base N
Sheep	64.0	16.0	20.0
Goat	81.0	7.0	12.0
Cow	92.1	7.3	0.7
Horse	88.0	12.0	0.5
Pig	92.3	1.8	5.8
Dog	97.1	1.9	1.3
Man	2.0	90.0	8.0

Uric acid (largely in the form of sodium urate) is a constant constituent of blood, but in most mammals other than man the amount is small. In the blood of man a range of 0.7 to 3.7 mg. per 100 cc. is found, while in the blood of the rabbit, sheep, pig, horse, monkey, ox, and cat, the range is 0.05 to 0.2 mg. per 100 cc. (Folin and Denis). In birds the amount is even higher than in man.

Uric acid is derived from the metabolism of nucleic acid of the tissues or of the absorbed products of nucleic acid digestion (p. 344). The changes undergone in the conversion of nucleic acid and its derivatives into uric acid are complex and only partially understood. A number of enzymes are concerned in the reactions. For further details on these points, textbooks of biochemistry may be consulted.

Adenine, guanine, hypoxanthine, and xanthine are intermediary substances in the conversion of nucleic acid to uric acid and they appear in the urine in small amounts. Adenylic acid, adenosine, inosinic acid, and other intermediary substances in the metabolism of nucleic acid and its derivatives are concerned in the biochemical changes occurring during the contraction of skeletal muscle (p. 563).

As already noted, uric acid is, in the urine of most mammals, largely replaced by its oxidation product allantoin. However, in the urine of man and the chimpanzee allantoin is practically absent; and the Dalmatian dog is interesting in that apparently only about one-third of the uric acid of this animal is converted to allantoin, whereas in dogs generally the conversion is nearly complete. The inheritance of high uric acid excretion in dogs has been studied by Trimble and Keeler.

The place of conversion of uric acid to allantoin is the liver. This was shown to be true by complete removal of the organ in dogs, whereupon the destruction of uric acid, as revealed by blood analyses, stopped (Bollman, Mann, and Magath, 1925). The conversion of uric acid to allantoin is catalyzed by the enzyme uricase. Some animals lack uricase and are therefore unable to convert uric acid to allantoin.

The formation of uric acid in birds requires further notice. Unlike mammals, birds excrete most of their nitrogen in the form of uric acid (urates), for they have no ability to change ammonia to urea and they are unable to convert uric acid to allantoin. The uric acid of birds is formed from ammonia, which originates from amino acids. The liver appears to be the place of uric acid formation in the chicken.

Hippuric Acid. This is a compound of glycine and benzoic acid. The union of these substances to form hippuric acid may be represented as follows:

$$\underset{\text{Benzoic acid}}{C_6H_5 \cdot COOH} + \underset{\text{Glycine}}{CH_2 \cdot NH_2 \cdot COOH} = \underset{\text{Hippuric acid}}{C_6H_5CO \cdot NHCH_2 \cdot COOH} + H_2O.$$

Hippuric acid occurs in the urine of all mammals, but the amount in that of carnivores is small, while the amount in that of herbivores is comparatively large. In the urine of the dairy cow, Healy found a hippuric acid content of 0.01 to 4.15 per cent, with an average of 1.17 per cent. In the urine of the camel Read reports that the amount of hippuric acid is large and is comparable to the amount found in the urine of cows and horses. In the urine of the mule this same investigator found an average hippuric acid content of 1.08 per cent.

Hippuric acid represents a form in which the body gets rid of benzoic acid when it occurs in the food or is formed in metabolism. The body is unable to oxidize benzoic acid; therefore in order to detoxicate it and prepare it for excretion by the kidney it is conjugated with glycine (and to some extent with glucuronic acid). The place of formation of hippuric acid probably varies in different species. In all animals it appears that the kidney itself is one seat of its formation, while in some animals the kidney is the sole seat. The surviving kidney of the dog, pig, sheep, and man is capable of forming hippuric acid from sodium benzoate and glycine. The dog is unable to form hippuric acid after double nephrectomy, although in other animals its formation may take place in all tissues (Snapper, Grünbaum, and Neuberg). The liver may be an important place of its formation in some species.

Amino Acids. A small amount of the nitrogen of the urine is present in the form of amino acids. They and their derivatives occur in urine probably because of the inability of the kidney to completely prevent their leaving the blood. This does not apply to glycine in conjunction with benzoic acid. This combination, hippuric acid, is an excretory product.

Sulfur-containing Constituents. Urine is an excretion for the elimination not only of nitrogenous but also of sulfur-containing wastes. Sulfur occurs in the urine in two forms, as unoxidized or neutral sulfur and as oxidized sulfur. Unoxidized or neutral sulfur is contained in such compounds as cystine, cysteine, methionine, taurine, and ethyl sulfide and is mainly of tissue origin. As indicated elsewhere (p. 420), the neutral sulfur elimination tends to increase with the 0.73 power of body weight. Oxidized sulfur occurs in the urine in the form of sulfates, of two kinds: inorganic sulfates of sodium, potassium, calcium, and magnesium, and ethereal sulfates. Most of the urinary sulfates arise from the oxidation of cystine and methionine in the body. A smaller amount comes from the sulfates in the food. The relation of ethereal sulfates to intestinal putrefaction is discussed on p. 356.

Inorganic Salts. The inorganic salts of the urine comprise mainly chlorides, sulfates, phosphates, and bicarbonates of potassium, sodium, calcium, and magnesium. Traces of fluorides, silicates, iron, copper, manganese, iodine, zinc, and other inorganic substances may be found in some urines.

In dairy cows Keitt found the average daily sodium chloride excretion in the urine to be about 121 gm. Hayden reports that chlorides are found in the urine of dairy cows to the extent of 0.3 to 0.5 per cent; sulfates, 0.2 to 0.3 per cent; phosphates, a trace or none. Bicarbonates occur in the urine of herbivores in relatively large amounts. They are chiefly responsible for the alkalinity of such urine.

Urinary Pigments. The principal pigment of the urine is urochrome. It is composed of a peptide and urobilin. Traces of urobilin and other pigments are found.

Pathological Constituents.[1] It is usually stated that the presence of albumin, glucose or similar carbohydrate, bile pigments and bile salts, blood, and the ketones in urine is pathological. The more sensitive tests indicate that this is not strictly true; some of these substances may be present in traces even in normal urine.

Sugar, probably lactose, is often present in the urine of the cow, especially soon after parturition and during the early stage of lactation (Boddie, Sampson). Ketone substances (acetone, acetoacetic acid, and ß-hydroxybutyric acid) may be present in the urine of normal pregnant or lactating cows to the extent of about 15 mg. (expressed as acetone) per 100 cc. The average, however, is about 7 mg. per 100 cc. (Sampson and Hayden). Much less than this amount—a mere trace—is found in the urine of nonlactating and nonpregnant cows (Boddie). Only traces of the ketone substances are present in the urine of normal sheep (Dimock, Healy, and Bullard; Roderick and Harshfield; Sampson and Hayden).

It is a well-known fact that the dog is very resistant to the development of ketosis; hence the usual qualitative tests for acetone and acetoacetic acid on the normal urine of the dog are generally negative.

THE URINE OF THE CHICKEN

The glomeruli of the kidney of birds are poorly developed as compared with those of mammals (Marshall, 1934). This suggests that tubular excretion is well developed in the kidney of the bird, and certain experiments on this question in the chicken support this view (Pitts).

The osmotic pressure of urine obtained from the ureter of the chicken (ureteral urine) may be much less than that of blood or somewhat more. Expressed as a percentage of NaCl, osmotic pressures ranging from 0.13 to 1.3 per cent have been obtained (Korr).

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[1] Contributed by Dr. J. Sampson.

Korr describes ureteral urine of the chicken, at different rates of flow, as follows: During a high flow (diuresis), the urine is usually clear. When the flow is moderate, the urine is somewhat cloudy. At a low flow, it is thick, slimy, and yellow. Normally uric acid deposits cause the urine to be cloudy. Korr calculated from his own data and those of other workers that the amount of urine entering the cloaca of the chicken may be as much as 700 cc. in 24 hours. Of this, only a few cubic centimeters are excreted from the cloaca, usually in a semisolid form. The absorption of water from the urine entering the cloaca appears to be a function more of the rectum than of the cloaca, urine passing into the rectum from the cloaca by regurgitation. The absorption of water is accomplished without osmotic work, presumably by the simultaneous absorption of chloride and other substances.

The view that the ureteral urine of the chicken is copious in amount and that concentration of this urine occurs in the cloaca (or rectum) is not universally held. In the experiments of Hester, Essex, and Mann, the largest amount of urine obtained from exteriorized ureteral orifices of chickens during periods up to 24 hours in duration was 124 cc. They believe that normal ureteral urine of the chicken is already in a concentrated state and that the cloaca is a collecting organ analogous to the bladder of mammals. They point out that short periods of observation of urine secretion in birds may be unreliable because of the considerable diuresis often induced by the disturbance of the bird. "The normal urine of birds is a cream-colored, thick, tenacious mucoid material containing an abundance of urates which readily settle out forming a semisolid mass. The pH of samples taken under different experimental conditions varied from 6.22 to 6.7" (Hester, Essex, and Mann). The experiments of Hart and Essex support the view that the volume of ureteral urine in the chicken is small. They believe that absorption of electrolytes and of some water of the urine occurs in the rectum.

Chapter XXI

THE SKIN

THE skin consists of two principal layers: an inner layer of connective tissue, containing blood vessels, nerves, and lymphatics known as the dermis or corium, and an outer layer of nonvascular squamous epithelium known as the epidermis or cuticle. Four epidermal layers are recognized. The stratum germinativum, the deepest, is the layer where regeneration occurs. It contains three types of cells: germinal, spinous, and melanoblasts, which are believed to form melanin. The stratum granulosum, a thin layer of cells, is evident only where the epidermis is thickened. The stratum lucidum is also very thin and is not visible unless the skin is thick. The cells making up this layer are dead. The stratum corneum, the outermost layer, is composed of flattened, dry, dead cells, which are continually exfoliated in warm-blooded animals.

GENERAL FUNCTIONS

The main functions of the skin may be stated as follows: (1) It affords mechanical protection to the underlying parts. This applies particularly to the epidermis—whose outer layers are dead—in relation to the highly sensitive dermis. Wherever the chances of injury by external factors are greatest, the cornified layer of the epidermis is thickest. Hair, hoof, nails, and feathers, structures derived from, and built on much the same plan as the epidermis, enhance the mechanical protection afforded by this layer of the skin. (2) The epidermis protects underlying parts by preventing or limiting the penetration of many substances. (3) Protection against light is afforded by the skin because of the presence of the pigment melanin in the cells of the epidermis and the intercellular spaces of the dermis. It is the ultraviolet radiation that is absorbed by melanin. This pigment is believed to be formed in the melanoblasts of the stratum germinativum by the action of certain enzymes on tyrosine, or on a tyrosine derivative, dioxyphenylalanine or "dopa." Melanin is then thought to be discharged into the intercellular spaces of the dermis from which it can be taken up by other cells and stored. The effects of sunlight on the skin are considered in a recent review by Blum. (4) Regulation of body temperature is a function of the skin, which, together with the fat-containing subcutaneous tissue, constitutes a blanket that helps to prevent excessive radiaion and conduction of heat. Hair and feathers, in addition to affording mechanical protection, assist in heat retention by retarding air currents. The evaporation of sweat from the surface of the skin aids in heat loss. Changes in blood flow through the skin influence heat elimination; dilatation of the blood vessels of the corium increases the amount of heat lost, while vasoconstriction has the opposite effect. (5) By reason of the secretion of sweat and sebum, the skin is an organ of excretion. (6) The formation of vitamin D from cholesterol or some closely related compound by the action of ultraviolet radiation occurs in the skin and is one of its important metabolic functions. (7) The skin is an organ of respiration, although its importance in this respect is not the same in all animals. In the frog the absorption of oxygen and the elimination of carbon dioxide by the skin may be sufficient to maintain life after removal of the lungs. In mammals the skin is not an important respiratory organ. (8) The skin is a sensory structure placed between the organism and its environment, bringing the former into relationship with the latter. This function is performed by receptors of touch, warmth, cold, and pain in the epidermis and dermis.

Some of the functions of the skin enumerated above require further attention at this time or later. To this end, permeability and the secretory activities of the skin will be studied here; vitamin D will receive further notice in Chapter XXVI; the regulation of body temperature will be presented in Chapter XXVII; cutaneous sensations will be considered in Chapter XXX.

PERMEABILITY OF SKIN

The normal skin allows the passage through it of insignificant amounts of most liquids and some gases that come in contact with its outer surface. The fatty substances covering the surface of the skin, the keratin in the superficial cells, and the activity of the living cells of the deeper layers all contribute to this end. The last factor is probably the most important.

In general it may be said that the skin is impermeable or only slightly permeable to water and electrolytes, but that lipid-soluble substances can enter the living cells of the skin. The impermeability of the skin to water and electrolytes is a function of the "transitional layers between cornified and noncornified epithelium" (Rothman and Flesch). The lipid solubility of a substance is regarded as an important factor regulating skin permeability. If the substance is both lipid-soluble and water-soluble (alcohol, acetone, etc.), it may be expected to penetrate the skin, at least to some extent.

The absorption of gases by the skin has been frequently investigated. Many gases can penetrate the skin, some of them (hydrocyanic acid and apparently hydrogen sulfide) in sufficient amounts to cause poisoning or death (Walton and Witherspoon; Calvery, Draize, and Laug). However, carbon monoxide appears not to be absorbed by the skin. There is some penetration of the skin by heavy metals.

Permeability of the injured skin is another matter. There is no doubt that the functional alterations of the skin seen in such conditions as inflammation, vesication, mechanical trauma, etc., may affect permeability.

The subject of skin permeability is considered in a recent comprehensive review by Calvery, Draize, and Laug. It is evident from this study of the literature that much more research work will have to be done before numerous questions in this area can be given a satisfactory answer.

SEBACEOUS GLANDS AND THEIR SECRETION

Sebaceous glands, compound saccular in type, open for the most part into hair follicles. However, in some locations, as the lips, eyelids, vulva, glans penis, and prepuce, they open upon the free surface of the skin.

Sebum. The secretion of the sebaceous glands is known as sebum, and is an oily semiliquid material which solidifies upon exposure to air. It consists mainly of esters, not of glycerol, but of the higher alcohols including cholesterol. It is therefore not a true fat. Wool fat or lanolin is a similar substance that may be extracted from wool. It consists mainly of a mixture of esters of cholesterol and esters of alcohols of the fatty series. The fatty acids found in these esters appear to be cerotic, palmitic, and stearic (Röhmann). The full significance of sebum is not understood. It doubtless aids in preventing the penetration of harmful substances into the skin, it affords protection against the disintegrating influence of external moisture, it gives pliability to the skin, and it contains precursors of vitamin D.

The tarsal glands, of the eyelids, and the glands of the prepuce are modified sebaceous glands. The ceruminous glands, of the external ear, resemble sweat glands in structure, though their secretion, cerumen, is related to sebum. It contains a brownish pigment. Cerumen acts to discourage the entrance of insects, and to prevent the passage of particles of inanimate matter, into the ear.

Secretion of Sebum. The traditional view regarding the secretion of sebum by the sebaceous glands is that their cells, instead of forming and discharging a secretion as gland cells do generally, undergo a process of degeneration and disintegration to form sebum. The outer layers of the gland cells multiply very rapidly, pushing the newly formed cells toward the center of the sacculi. When the cells are pushed far enough inward to begin to suffer from lack of nutrition, they degenerate and disintegrate, the products of these metamorphoses being sebum. The secretory process is continuous. Some recent work suggests that sebum is formed by true secretory activity of the gland cells. Evidence has been obtained which suggests that the secretory activity of the sebaceous glands is controlled by the nervous system (Rothman and Felsher).

SWEAT GLANDS AND THEIR SECRETION

The sweat or sudoriferous glands reach their highest development in man. Among the domestic animals they are best developed and most numerous in the horse, which animal sweats, as does man, from the general body surface. The sheep also sweats from the whole body surface, and the same is occasionally true of the ox. In "sweating sickness" of the calf, sweating may occur from the general body surface (Du Toit). In some domestic species, however, the active sweat glands are confined to certain skin areas, and in still others sweating does not occur at all. Thus the dog and cat sweat from the foot pads, the ox and pig mainly from the snout, and the goat and rabbit not at all. However, in the dog numerous sweat glands are found on the hairy parts of the body (Speed) and the drug pilocarpine may cause recognizable sweating from the hairy portions of the skin (Eimer).

Sweat glands are coiled or convoluted tubular glands, whose active portions lie in the subcutaneous tissue. After penetrating the dermis and epidermis the ducts open on the surface of the skin. In the dog the sweat glands that occur on the hairy parts of the body are simple uncoiled glands which open into hair follicles. Those occurring in the foot pads are coiled (Speed).

Composition and Significance of Sweat. The sweat of man is a clear liquid containing about 99 per cent of water and having a specific gravity of 1.001 to 1.006 (Schwenkenbecher). Its reaction is usually acid. The sweat of the horse is alkaline in reaction, having a mean *p*H of about 8.5 (Korkisch). Smith (1890) found filtered sweat of the horse to have a reddish-yellow color, a strongly alkaline reaction, and a specific gravity of 1.020. The composition was found to be as follows: water, 94.38 per cent; organic matter, 0.53 per cent; ash, 5.09 per cent. The organic matter consisted mainly of serum albumin and serum globulin. Even larger amounts of protein in the sweat of horses were found by Ritter, who reported a range of 1.95 to 3.47 per cent and a mean of 2.75 per cent. The urea content was found to vary from 0.11 to 0.16 per cent, with a mean of 0.14 per cent. The significance of the large amount of protein in the sweat of horses is not known. Smith pointed out that it is a cause of loss of condition in animals that sweat too freely.

Sweat is a watery secretion poured out upon the surface of the body to assist, upon evaporation, in cooling the body. In man at least, it cannot be considered as an important excretion, for it is nearly all water. In the horse, on the other hand, its high inorganic salt content and its relatively high urea content require that it be regarded somewhat in the light of an excretion. In animals that sweat, a reciprocal relationship exists between the skin and kidneys in the elimination of water. In pathological conditions of the kidney the skin may take over a considerable share of that organ's work.

Loss of Water Through the Skin: Secretion of Sweat. Loss of water through the skin occurs continuously. Ordinarily, evaporation keeps pace with production, so that no visible moisture collects on the skin. This evaporated moisture is a part of the insensible water loss of the organism, and may be designated the *cutaneous insensible water loss.* Although this loss has long been recognized, it is not fully settled whether it is produced by the sweat glands themselves or is simply evaporated from the epidermis generally. That the latter view is probably correct is indicated by the observation that animals not possessing sweat glands lose some water through the skin. Furthermore human subjects in whom sweat secretion is experimentally suppressed in regions of the skin still show an insensible water loss from those regions. Diffusion of water vapor through the outer layers of the epidermis probably accounts for the cutaneous insensible water loss (Pinson).

At times water is poured out on the surface of the skin at a faster rate than it can be removed by evaporation, whereupon visible droplets termed sweat collect. There is no question that this moisture is produced by the activity of the sweat glands.

The secretion of sweat is under the control of secretory nerve fibers, which leave the spinal cord in the thoracolumbar outflow constituting the sympathetic system. That the secretion may be brought about by nervous influences may be shown by electrical stimulation of the peripheral end of the sciatic nerve in the cat or dog. The stimulation causes visible droplets of sweat to appear on the foot pad. That such a production of sweat is not caused by an increase in the blood supply but by the action of secretory nerves is shown by the fact that the secretion can occur after the blood supply to the limb is completely shut off. Furthermore the sweat glands can secrete against a higher pressure than the capillary blood pressure in the glands.

The sweat nerves are controlled by sweat centers located in the central nervous system. The centers may be aroused to activity (1) by afferent impulses arising in the skin from heat stimulation; (2) by an increase in temperature of the blood flowing through the sweat centers; (3) by a change in the composition of the blood such as an increase in the carbon dioxide content or the hydrogen ion concentration; and (4) by various psychic states, as anticipation, fear, and anxiety.

Probably the second is the chief way in which the centers are normally activated. Blood flowing through active organs, as liver and muscle, may have its temperature raised by metabolism, or under some conditions blood flowing through the skin may have its temperature increased by the action of external heat. Blood derived from any of these sources under the conditions mentioned might, during its passage through the sweat centers, arouse them to action.

A number of *drugs* cause sweating when injected into animals. In the cat pilocarpine causes the secretion of sweat by peripheral stimulation whereas atropine stops the secretion by paralyzing the mechanism stimulated by pilocarpine. These are unusual effects, for in most situations pilocarpine and atropine act on the parasympathetic nerves, and not on the sympathetic as in the present instance. The evidence indicates that the sweat secretory fibers in the cat are cholinergic—that is, lead to the production of acetylcholine—and not adrenergic as would be expected from their sympathetic distribution. The situation in man (Dale and Feldberg) and in the dog is believed to be similar to that in the cat. Adrenaline fails to cause sweat secretion in the cat whereas it is effective in the horse (Langley and Bennett) and sheep. This leads to the belief that the sympathetic fibers to the sweat glands in the latter animals are adrenergic.

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PART VI

Metabolism and Heat Regulation

Chapter XXII

THE EXCHANGE OF MATTER AND ENERGY

THE foodstuffs, prepared by digestion for absorption, pass into the blood and are transported to the body tissues where they are utilized for growth and repair or for energy. Oxygen, absorbed by the lungs, plays a necessary part in many of the metabolic transformations and, strictly speaking, may be regarded as one of the foodstuffs. Lusk defined metabolism as the "chemical changes of materials under the influence of living cells." The chemical changes of metabolism are of two kinds: constructive or synthetic and destructive or analytic. The former changes are designated as anabolism, the latter catabolism. The term nutrition is sometimes used practically synonymously with metabolism, but as generally used it covers a broader field. In its broadest aspects, nutrition may be said to include all those processes whereby foods and oxygen are presented to and utilized by the living cells, and waste products are eliminated. According to this view circulation, respiration, digestion, absorption, metabolism, and excretion become the mechanisms of nutrition.

THE COMPOSITION OF THE ANIMAL BODY

From a chemical point of view the animal body is an extremely complex aggregate of many substances, organic and inorganic. From another standpoint, however, it may be conceived of as consisting of water, proteins, nonprotein nitrogenous substances, carbohydrates, fats and allied compounds (lipids), and minerals or ash.

Proteins. Although not unlike plant proteins in general properties, animal proteins show certain specific differences from plant proteins. Thus nucleic acids derived from animal nucleoproteins are distinctly different in several respects from those of vegetable origin; the amino acid content of the two kinds of protein may be very different quantitatively; and animal proteins have a lower nitrogen content than vegetable proteins. Armsby and Moulton have compiled in their monograph the analyses of many animal proteins.

Nonprotein Nitrogenous Compounds. In animals, as in plants, nonprotein nitrogenous compounds occur in great variety. In animals one finds lecithin, urea, creatine, creatinine, uric acid, xanthine, hypoxanthine, and many amino acids and other compounds arising during the digestion and metabolism of protein. Quantitatively the protein of the body so far exceeds the nonprotein nitrogenous substances that for some purposes all the nitrogenous matter may be considered as essentially protein. True protein and nonprotein nitrogenous compounds together may be designated as crude protein (N × 6.25).

Carbohydrates. The carbohydrate content of the plant organism is generally large, whereas that of the animal organism is small. Glycogen, found in the liver and muscles; glucose, found in blood and lymph; and lactose, found in milk, are the main carbohydrates of the animal.

Fats. Whereas most plants store their potential energy by the deposition of carbohydrate, animals store theirs mainly in the form of fat. In mice, for instance, the storage fat may have twenty times the energy value of the storage carbohydrate, and in chicks fifty times (Pryde). When referring to the ether-soluble constituents of the living organism, the term lipid is preferable to the term fat; for the former term includes not only the true fats (esters of fatty acids with glycerol) "but also all types of compounds in which fatty acids occur or with which fatty acids may be associated in the cell." Examples of lipids, other than true fats, are waxes, the phospholipids (phosphatides) lecithin, cephalin, and sphingomyelin, the galactolipids or cerebrosides, fatty acids, and sterols.

Ash. The composition of the ash of the body is exemplified in the accompanying tables (Hogan and Nierman).

PERCENTAGE COMPOSITION OF ASH OF CALF, MEDIUM IN NUTRITION

Na_2O	K_2O	CaO	Fe_2O_3	MgO	P_2O_5	Cl	SO_3	SiO_2	CO_2
6.00	4.68	37.52	0.71	1.76	34.47	3.55	4.47	7.37	0.40

PERCENTAGE OF MINERAL ELEMENTS IN ENTIRE BODY OF FOREGOING CALF
(Fresh-weight basis of calculation)

Na	K	Ca	Fe	Mg	P	Cl	S
0.192	0.168	1.157	0.021	0.046	0.649	0.153	0.077

The Composition of the Entire Body. The following table will suffice to illustrate the composition of the entire animal body (Mitchell and Hamilton, 1927).

COMPOSITION OF ENTIRE EMPTY CARCASSES OF HORSES

Weight	Age	Sex	Composition				
			Dry Matter	Crude Protein	Fat	Ash	Ca
pounds	*years*		*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
1525....	22	Stallion	37.2	19.9	13.2	4.43	1.49
1700....	17½	Mare	39.9	16.8	16.7	4.52	1.46
1605....	5	Mare	37.2	17.8	12.4	5.03	1.70

Obviously the percentage of water which was present in these carcasses is 100 minus the percentage of dry matter and is in case of numbers 1 and 3, 62.8 per cent and of number 2, 60.1 per cent. Because of the variability of the fat content of the body, the composition of the body is sometimes expressed on a fat-free basis. Extensive compilations of the composition of animals may be found in the monograph by Armsby and Moulton.

THE BALANCE OF MATTER AND ENERGY

All the energy displayed by the animal body—heat, mechanical energy, electrical energy—comes from the oxidation of the organic foodstuffs: carbohydrate, protein, and fat. Water, inorganic salts, and vitamins, necessary as they are, do not supply energy to the body. When the energy-producing foodstuffs are burned in the body, the latent or potential energy locked up in their molecules is released and serves to supply the animal with its energy requirements. The potential energy of the food comes from the sun, whose energy, in the presence of chlorophyll, is used to build up sugar from carbon dioxide and water. Whenever the sugar is oxidized to carbon dioxide and water, the same amount of the sun's energy stored in it is set free.

One method of assessing the nutritional status of an animal is to perform a balance experiment, that is, to determine the difference, if any, between the income and outgo of matter (balance of matter) or the difference between the income and outgo of energy expressed as Calories (balance of energy).

The Balance of Matter. In determining the balance of matter, one compares the income in the food with the outgo in the excretions of the particular substance under observation. Measurements of balances of matter are usually limited to mineral substances, nitrogen, and carbon.

The Mineral Balance. The gain or loss of inorganic matter by the body may be determined by comparing the mineral content of the food over a given period of time with that of the urine and feces (and milk) during the same period. In the accompanying table the annual mineral balances of sodium, potassium, calcium, magnesium, phosphorus, and chlorine of a cow are shown. It is evident that the balances of sodium and calcium are negative, the body having lost more of these elements than it gained, whereas the balances of potassium, magnesium, phosphorus, and chlorine are positive.

Annual Mineral Balance of Cow

(During the year the cow lost 49.2 kg. in weight)

	Income	Outgo			Balance
		In Milk (324 days)	In Excreta	Total	
	grams	*grams*	*grams*	*grams*	*grams*
Sodium	15,559.0	3,457.2	12,155.7	15,612.9	− 53.9
Potassium	40,618.2	10,155.3	30,283.7	40,439.0	+179.2
Calcium	38,941.6	7,061.3	32,819.1	39,880.4	−938.8
Magnesium	13,156.0	804.8	12,235.9	13,040.7	+115.3
Phosphorus	15,017.3	6,366.1	8,570.9	14,937.0	+ 80.3
Chlorine	27,204.8	7,154.0	19,290.3	26,444.3	+760.5

(Data of Forbes, 1935.)

Nitrogen Balance. When protein is metabolized carbon dioxide, water, and a number of nitrogenous waste products are formed. The latter substances, of which urea is the most important, are eliminated mainly in the urine but to a small extent in the feces, sweat, hair, and dandruff. By determining the nitrogen content of the food and of the excreta and comparing the results, the nitrogen balance may be ascertained. This indicates whether the body is gaining or losing protein.

The table on the next page showing the nitrogen balance of a steer (Armsby and Moulton) may be cited in illustration of these statements. It is seen that there was a nitrogen balance of 17.37 gm. in favor of the excreta. The animal therefore lost this amount of nitrogen from the body and showed a negative nitrogen balance. If it is desired to express the nitrogen balance in terms of protein, this may be done by multiplying the number of grams of nitrogen by 6.25, the average nitrogen content of protein being 16 per cent.

Daily Nitrogen Balance of a Steer

Nitrogen	Income	Outgo
	gm.	*gm.*
In hay	71.40	
In feces		28.40
In urine		58.50
In brushings*		1.87
Loss from body	17.37	
Total	88.77	88.77

* May be omitted.

Nitrogen Equilibrium. A fasting animal continues to give off nitrogen in the excreta. This nitrogen is derived from tissue metabolism, which is greater during fasting because then the energy of the body comes, not from ingested food, but from stored food and from tissue destruction. It might be supposed that in order to balance the nitrogen loss of fasting by the nitrogen of the food it would be only necessary to give the animal an amount of protein equivalent to the nitrogen excretion, but experiments on dogs that were made to fast and then were fed only protein show that more than three times the amount of protein corresponding to the fasting nitrogen loss is necessary. At about this level of protein intake the nitrogen output equals the nitrogen intake, and the animal is said to be in nitrogen equilibrium. If carbohydrate or fat is now added to the diet the protein intake can be greatly reduced without the animal's showing a negative nitrogen balance. The reduction may be so great, in fact, that the nitrogen of the protein intake approaches in amount the nitrogen of the fasting catabolism. The foregoing, however, does not apply to omnivorous and herbivorous animals, for it is not possible to bring these animals into nitrogen equilibrium on protein food alone. They seem to be unable to digest enough protein.

If after nitrogen equilibrium has been established the protein intake is further increased, there is shortly a corresponding increase in nitrogen output, equilibrium simply having been established at a higher level. The figures in the table on p. 438 illustrate this point. The animal, in nitrogen equilibrium while receiving 154 gm. of nitrogen, continued in nitrogen equilibrium when the intake was increased to 213 gm. Mature animals of all classes when properly nourished remain in nitrogen equilibrium for long periods of time. Growing and convalescent animals obviously cannot be in nitrogen equilibrium, for they are laying down protein in their tissues; they are in a condition of positive nitrogen balance.

RELATION OF NITROGEN INTAKE TO NITROGEN OUTGO

Days of Experiment	N of Food	N of Excreta
	gm.	*gm.*
1–7	154.8	153.0
8–17	213.7	213.3

As stated above, if an animal (dog) is brought into nitrogen equilibrium on protein alone, it is found that a large amount of the food protein can then be replaced by carbohydrate or fat, or a mixture of these, and the animal will still remain in nitrogen equilibrium. There is a point, however, below which the protein intake cannot be reduced if the animal is to remain in nitrogen equilibrium. The explanation as to why carbohydrate or fat can to a large extent replace protein in metabolism lies in the fact that much of the food consumed goes to meet the energy needs of the organism, and that any one of the three energy-producing foodstuffs, protein, carbohydrate, and fat, suffices for this purpose if the replacement is made with due regard to caloric contents. The reason why carbohydrate or fat cannot completely replace protein is that a certain amount of the latter is absolutely necessary for the formation of substances required in the intermediary metabolism. Creatine and the purines, from which creatinine and uric acid are formed, are instances. The manufacture of certain hormones may be another case in which a supply of protein is essential. These requirements help to account for the *minimum protein catabolism*. In the new knowledge of protein metabolism less significance is attached to a quota of protein formerly supposed to be required to replace tissue wear and tear. It is now held that the dynamic interchanges of amino acids continually occurring in the tissues involve little actual loss of nitrogen from the tissues.

Carbon Balance. This may be determined by comparing the total income of carbon over a period of time with its total outgo. Evidently, in the carbon outgo, account must be taken not only of the carbon in the urine and feces but also of the carbon in the gaseous excreta. In herbivores these include not only carbon dioxide and methane eliminated through the lungs but also these same gases derived directly from the alimentary canal, as by belching. In carnivores and man the carbon dioxide of the expired air is the only gaseous carbon-containing compound that need be considered. The methods of determining the amount of the gaseous excreta will be discussed later.

From the carbon and nitrogen balances the gain or loss of fat by the body may be calculated. The accompanying table and calculations, from Armsby and Moulton, serve to illustrate the nitrogen and carbon balances of a steer and to show how the gain or loss of body fat may be computed from these. In the experiment and calculations it was assumed that the carbohydrate content of the body underwent no significant change.

Daily Nitrogen and Carbon Balances of a Steer

	Nitrogen		Carbon	
	Income	Outgo	Income	Outgo
	gm.	*gm.*	*gm.*	*gm.*
6988 gm. timothy hay...	**56.4**		**2831.7**	
400 gm. linseed meal...	**21.9**		**172.6**	
16619 gm. feces..........		**33.5**		**1428.7**
4357 gm. urine.........		**32.4**		**124.2**
37 gm. brushings.....		**1.3**		**8.0**
4730 gm. carbon dioxide.				**1290.2**
142 gm. methane......				**106.6**
Gain by body.......		**11.1**		**46.6**
Total...........	**78.3**	**78.3**	**3004.3**	**3004.3**

The steer therefore showed a positive nitrogen balance of 11.1 gm. and a positive carbon balance of 46.6 gm. Since the average body protein of cattle contains 52.12 per cent of carbon, and the average fat of animals 76.5 per cent of carbon, the computation of the gain of fat in the instance of this steer is as follows:

Total carbon gained 46.6 gm.
Gain of protein, 11.1 gm. N × 6.25 = 69.4 gm.
Carbon gained as protein 69.4 × 0.5212 gm. = 36.2 gm.

Carbon gained as fat 10.4 gm.
Fat equivalent, 10.4 ÷ 0.765 = 13.6 gm.

The gain of fat was therefore 13.6 gm.

The Balance of Energy. *Units of Heat.* The unit of heat is the calorie (cal.), which is the amount of heat required to raise the temperature of one gram of water one degree C. The large calorie or kilocalorie (Cal.) is equal to 1000 cal. and is the unit commonly used in physiological work. One Calorie equals 427 kilogram-meters. Another unit, the Therm, is sometimes used in computations dealing with large animals. It is equivalent to 1000 Cal.

Heat Values. When carbohydrates and fats are oxidized in the body, they yield the same end-products, carbon dioxide and water, as when burned outside the body. Therefore the amount of heat given off in the two combustions is the same per unit of weight of the substances and is, on the average, for a gram of carbohydrate 4.1 Cal. and for a gram of fat 9.3 Cal. Proteins, on the contrary, cannot be oxidized as completely in the body as outside. Hence they yield a smaller amount of heat in the body than outside. This is because a number of protein derivatives, the most important of which is urea, escape oxidation in the body and are eliminated in the excreta, whereas outside the body they are capable of being completely burned. The heat value of a gram of protein when metabolized inside the body is, on the average, 4.1 Cal., and is only 75 per cent as great as its heat value when burned outside the body; the remaining 25 per cent of energy is lost to the body.

Income of Energy. As previously stated, the energy of the animal body is derived, by oxidation, solely from the chemical energy of the foods. The total or gross energy of the food, as determined by its heat of combustion in some form of calorimeter (bomb calorimeter), is the *gross income of energy* of the body, and for convenience it may be expressed as heat, although of course when it is liberated by oxidation in the body some of it may appear as mechanical work.

The *urine,* because it contains a number of substances (urea, etc.) capable of being further burned in the calorimeter, is a source of energy loss to the body of all animals. The *feces* likewise contain materials that are capable of further combustion. This is particularly true of the feces of herbivores because of the relatively low digestibility of their foods. In addition, in herbivores *combustible* gases, mainly methane, formed by fermentation in the alimentary canal and eliminated from the body, must be taken into account. They are of no account in carnivores and man. The potential energy of the feces, urine, and combustible gases must therefore be determined, and this can be done by collecting these substances and measuring their heats of combustion. Finally, the increase in heat production that accompanies and follows feeding must be considered. This *heat increment* or *calorigenic effect* is lost to the body except in cold weather, when it is of use in keeping the animal warm. The method of determining the calorigenic effect, as well as its cause, will be mentioned later.

On typical rations herbivorous animals (cattle, rabbits) lose in the feces about 28 per cent of the gross income of energy, in the urine about 5 per cent, and in the combustible gases about 9 per cent. All of these losses tend to increase with increases in the plane of nutrition but the changes are usually not very great. The loss attributable to the heat increment of feeding, however, varies greatly with the plane of nutrition. The range is from approximately 3 per cent of the gross energy when the animal is on a half-maintenance ration to about 20 per cent when the food intake is maximal (Brody and Proctor).

The sum of these four energy losses must be deducted from the gross income of energy. The difference is the *net income of energy.*

Outgo of Energy. This can be expressed as heat and can be determined either directly, by measuring the heat elimination, including the latent heat of water vapor, in a calorimeter, or indirectly, by calculations based on the oxygen consumption and the carbon dioxide production of the animal. The former method of determining heat production is known as direct calorimetry, the latter as indirect calorimetry.

By comparing the net income of energy with the outgo of energy, it is possible to determine whether there has been a gain or loss of energy by the body.

For further information on nutritional balances, particularly as applied to farm animals, the book by Maynard is recommended.

INDIRECT CALORIMETRY

The amount of heat produced in the body can be calculated from the gaseous metabolism, as determined with some form of respiration apparatus. This is the method of indirect calorimetry. In general, two types of respiration apparatus are available for this purpose: the open-circuit and the closed-circuit types.

Open-Circuit Types. 1. The original open-circuit respiration apparatus was designed by Pettenkofer. The animal, inclosed in a chamber, breathes in a continuous current of outdoor air, the amount of which is determined by passage through a gas meter. Continuous samples of air are taken at the points of entrance and exit. From these samples and the total amount of air passing through the chamber, the oxygen consumption and carbon dioxide production can be calculated.

2. Haldane's modification of the Pettenkofer method is well adapted for small animals. It is a gravimetric method. The apparatus (Fig. 102) consists of a chamber for the animal, an ingoing chain of absorber bottles, an outgoing chain, a gas meter, and a pump. Air entering the animal chamber is made free of water vapor and carbon dioxide by passage through sulfuric acid and soda lime or caustic alkali. The outgoing air contains water vapor and carbon dioxide derived from the animal. These are absorbed by appropriate reagents. The carbon dioxide production is determined directly by the gain in weight of the carbon dioxide absorber of the outgoing chain; the oxygen consumption,

indirectly by the gain in weight of the water and carbon dioxide absorbers less the loss in weight of the animal and chamber—the insensible loss.

The oxygen determination is based on the long-known principle that the insensible loss of an animal equals the weight of the gaseous outgo minus the weight of the gaseous income. Since it is assumed that carbon dioxide and water vapor are the only gaseous excreta of significance, and the gaseous income is oxygen, it is evident that—

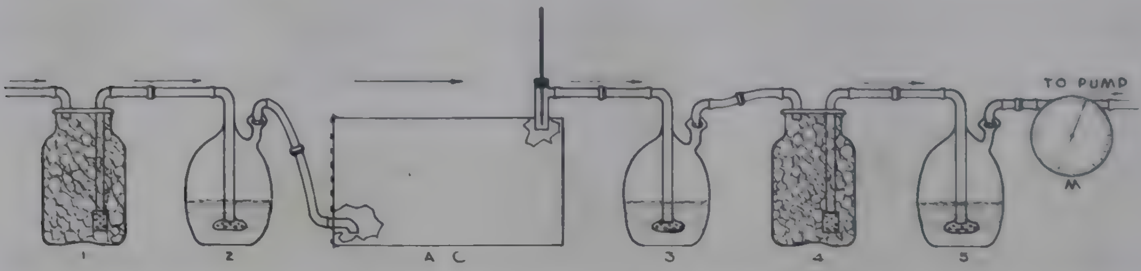

FIG. 102.—Diagram of the Haldane respiration apparatus. A.C., animal chamber; M, meter for measuring the rate of ventilation. Bottles 1 and 4 contain soda lime (or caustic alkali), for absorption of carbon dioxide. Bottles 2, 3, and 5 contain sulfuric acid, for absorption of water. Air entering the animal chamber is freed of carbon dioxide and moisture by passage through bottles 1 and 2. The animal gives off carbon dioxide and moisture, and these are collected in the bottles of the outgoing chain. Bottle 5 is necessary because soda lime gives off moisture. The gain in weight of bottles 4 and 5 represents the carbon dioxide production. The gain in weight of bottles 3, 4, and 5 minus the loss in weight of the animal and chamber represents the oxygen consumption.

$$\text{Insensible loss} = (H_2O + CO_2) - O_2$$

and that—

$$O_2 = (H_2O + CO_2) - \text{Insensible loss.}$$

An example may be given showing the calculation of the oxygen consumption. During a 4-hour period in a Haldane chamber a hen showed a total insensible loss of 13.50 gm., an insensible water loss of 10.05 gm., and a carbon dioxide production of 12.82 gm.

$$\begin{aligned} O_2 &= (10.05 + 12.82) - 13.50 \\ &= 9.37 \text{ gm.} \end{aligned}$$

3. Some open-circuit types of apparatus do not utilize an animal chamber but are equipped with a mask for the face or a tube for insertion into the trachea, appropriate valves, and a spirometer or a collapsible bag for collecting the expired air. The volume of collected air is determined by passage through a gas meter, or by direct reading if a spirometer is used and samples of it are analyzed for their oxygen and carbon dioxide contents. Knowing the composition of the inspired

air, the oxygen consumption and carbon dioxide production can be calculated.

Closed-Circuit Type. This type of respiration apparatus was devised by Regnault and Reiset. In it the animal breathes in a closed space, the carbon dioxide being absorbed by a suitable reagent and the oxygen being replaced from an oxygen tank. Thus the carbon dioxide production and the oxygen consumption can be determined. The closed-circuit apparatus may be used without a chamber, in which case a mouthpiece or mask and a bag or spirometer are necessary. In some applications of this method the carbon dioxide determination, but not its absorption, is omitted (Fig. 103).

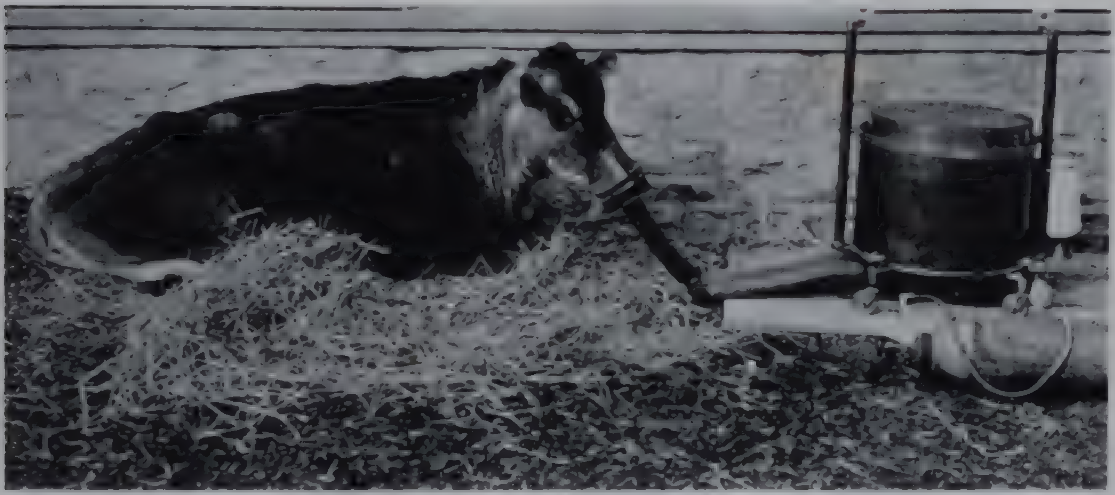

FIG. 103.—A method of measuring the energy metabolism (oxygen consumption) of animals. The face mask is connected with the spirometer by tubes for the expired air and the inspired air. Oxygen is introduced into the spirometer from the oxygen tank. The expired air is freed of carbon dioxide by passage through a can of soda lime in the apparatus. Valves cause the air to flow in one direction through the apparatus. As the oxygen is consumed the bell of the spirometer falls, and the rate of consumption is recorded on the kymograph at the right of the spirometer. Knowing the oxygen consumption (corrected for temperature and pressure) it is possible to calculate the metabolic rate. A mean respiratory quotient is assumed. (Brody, *Missouri Agricultural Experiment Station Research Bull.* 143, 1930.)

In herbivores when it is desired to determine not only the respiratory exchange and thus the metabolic heat production but also the energy given off in the gas methane, it is necessary to provide means for the determination of this gas.

DIRECT CALORIMETRY

In order to measure heat production directly, some form of calorimeter is necessary. Calorimeters have been devised for use with man and with animals of all sizes. A well-known type is the Atwater-Rosa calorimeter in its various modifications (Figs. 104, 105). This apparatus, like all calorimeters, measures the heat directly. As shown in Fig. 105, the heat produced is determined by the increase in the temperature of a known amount of water which flows in pipes through the chamber. Loss of heat from the calorimeter is prevented by wooden walls, dead air spaces, and an ingenious arrangement of thermocouples whereby any variation in the temperature of an inner and an outer wall of copper induces an electric current that activates a galvanometer. The observer then warms or cools the outer copper wall until the difference in temperature of the walls is corrected. The warming or cooling is accomplished by electric heaters or water tubes placed between the outer copper wall and the inner wooden wall.

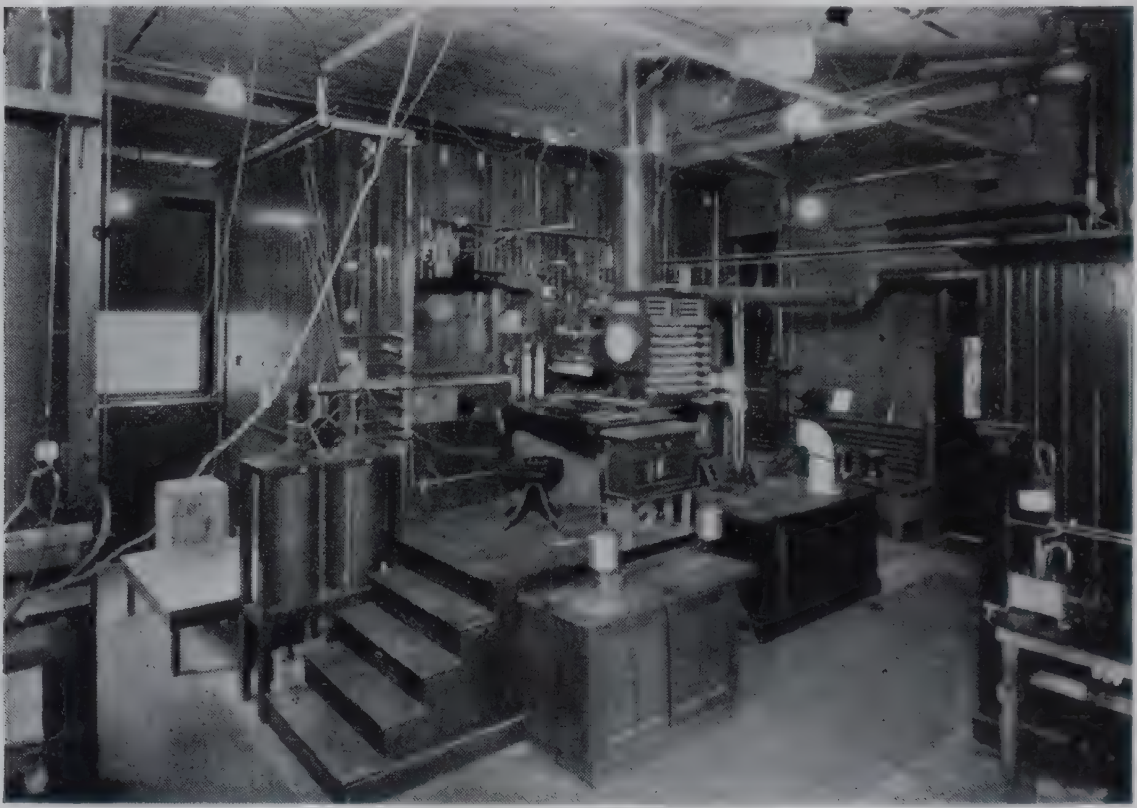

Fig. 104.—A respiration calorimeter for large animals; at the Institute of Animal Nutrition of The Pennsylvania State College. (Courtesy of Dr. E. B. Forbes.)

Since much of the heat given off from the body is in the form of latent heat of water vapor, it is evidently necessary to collect the water vapor produced by the animal in the calorimeter so that the amount of heat removed in this way can be calculated. The calorimeter is therefore equipped with means for absorbing water vapor (Fig. 105). The amount of heat required to vaporize a gram of water at the temperature of the body is approximately 0.58 Cal. In closed-circuit calorimeters provision must be made for absorption of the carbon dioxide produced by the animal and the replacement of the oxygen consumed. With these arrangements the calorimeter becomes a *respiration calorimeter,* and by its use it is possible to compare the results of direct and indirect calorimetry. Experiments show that the results are in very close agreement (Lusk).

A great deal of work has been done on calorimetry as applied to farm animals and an extensive literature is available. The following references will be of use to those who wish to find out what has been done: Armsby, Brody (1945), Ritzman and Benedict (1938), Paechtner, Krogh.

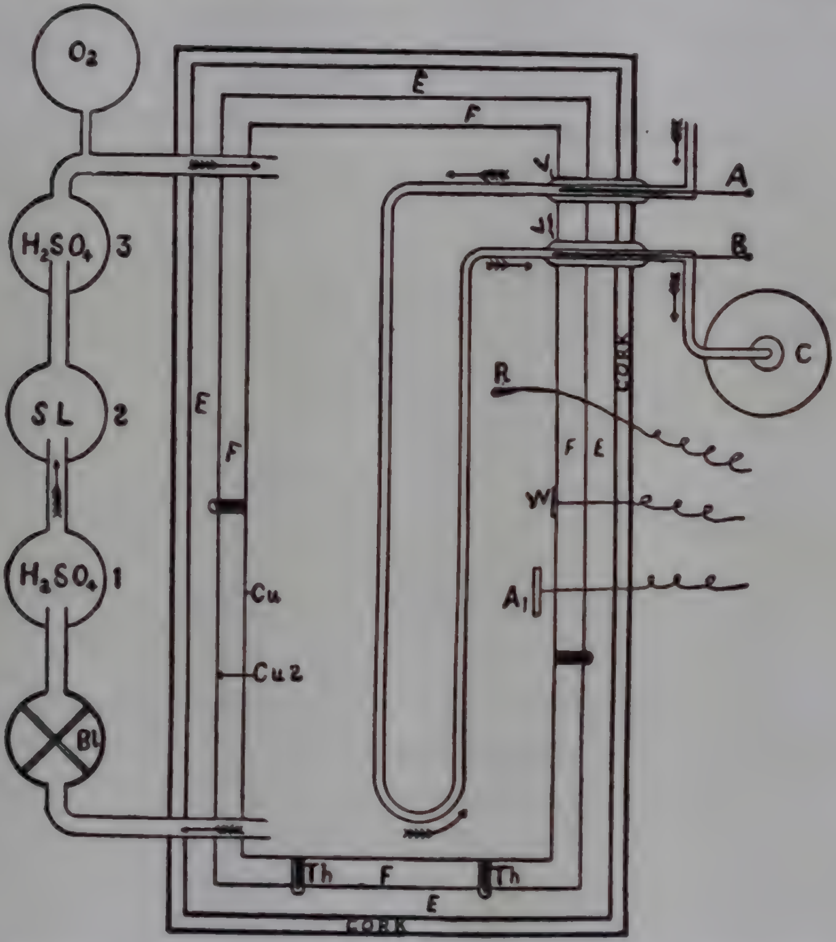

FIG. 105.—Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter. Bl, blower; 1, 2, 3, reagents for absorbing water vapor and carbon dioxide; O_2, tank for replacing the oxygen used; E, F, dead air spaces; Cu, Cu2, copper walls; Th, thermocouples; R, rectal thermometer; A1, thermometer for measuring the temperature of the air; W, thermometer for measuring the temperature of the wall; A, B, thermometers to record temperature of the ingoing and outgoing water, respectively; C, tank for weighing water that has passed through the calorimeter. (From Lusk's *Nutrition;* copyright—W. B. Saunders Company.)

THE RESPIRATORY QUOTIENT

A determination of the respiratory exchange involves measurements of the oxygen consumption and the carbon dioxide production. The ratio of the volume of carbon dioxide eliminated to the volume of oxygen absorbed is the respiratory quotient (R.Q.). Thus R.Q. $= \frac{\text{vol. } CO_2}{\text{vol. } O_2}$. The respiratory quotient finds its greatest usefulness in the information that it yields concerning the kind of foodstuffs being oxidized and in the calculations of indirect calorimetry.

Equimolar amounts of all gases occupy the same volume at standard temperature and pressure. The relation of carbohydrate and fat oxidations to the respiratory quotient will be apparent from a consideration of the following equations involving the oxidation of glucose and tripalmitin:

(1) $C_6H_{12}O_6 + 6O_2 = 6H_2O + 6CO_2$
Glucose

$$\text{R.Q.} = \frac{6 \text{ vol. } CO_2}{6 \text{ vol. } O_2} = 1.$$

(2) $C_{51}H_{98}O_6 + 72.5O_2 = 51CO_2 + 49H_2O$
Tripalmitin

$$\text{R.Q.} = \frac{51 \text{ vol. } CO_2}{72.5 \text{ vol. } O_2} = 0.703.$$

Evidently in the oxidation of a carbohydrate such as glucose all the oxygen goes to oxidize carbon, the volume of carbon dioxide excreted equals the volume of oxygen absorbed, and the R.Q. is 1; whereas in the oxidation of a fat such as tripalmitin the oxygen must go in part to the oxidation of carbon and in part to the oxidation of hydrogen, giving an R.Q. that is considerably less than 1, that is, 0.703. The generally accepted R.Q. for a mixture of fats is 0.707. It is therefore apparent that the size of the respiratory quotient is dependent not upon the species of animal but upon the nature of the foodstuff, or the mixture of foodstuffs, being oxidized by the animal. Owing to the nature of their customary foods, herbivores usually have a high quotient, carnivores a low quotient, and omnivores a quotient of intermediate value. In all animals that have been made to fast for any considerable period of time the R.Q. approaches 0.7, which indicates that the principal substance being oxidized is fat. This is illustrated in the accompanying table.

The R.Q. is sometimes greater than 1; this usually indicates the transformation of carbohydrate, which is oxygen-rich, into fat, which is oxygen-poor. The conversion of glucose into stearic acid may be represented, in its simplest form, as follows:

$$3C_6H_{12}O_6 = C_{18}H_{36}O_2 + 8O_2.$$

Effect of Fasting on the Respiratory Quotient

Sheep (Ritzman and Benedict)		Hen (Dukes)	
Hours after food	R.Q. (av.)	Hours after food	R.Q. (av.)
0–10	0.90	1–5	0.96
24–34	.76	22–29	.74
48–58	.72	48–53	.70
		72–78	.71
		88–101	.71

The oxygen thus released is used in the oxidative processes and correspondingly less oxygen is taken into the body from the air.

The combustion of protein in the animal body cannot be so simply represented as the combustion of carbohydrate or fat. It has been calculated that in the oxidation of protein 0.966 liter of oxygen yields 0.774 liter of carbon dioxide. The respiratory quotient of protein would therefore be $\frac{0.774}{0.966} = 0.801$. (For the details of the calculations reference may be made to the book by Peters and Van Slyke or by Lusk.)

In normal metabolism, energy is derived in part from the oxidation of each of the three classes of energy-producing foodstuffs. In order to make the complete calculations of indirect calorimetry, it is necessary to know not only the oxygen consumption and the carbon dioxide production but also the amount of the urinary nitrogen. From the last value the amount of protein burned (N × 6.25) and its caloric equivalent (grams of urinary N × 26.51 Cal.) may be computed, as may also the carbon dioxide production (grams of urinary N × 4.76 liters) and the oxygen consumption (grams or urinary N × 5.94 liters) attributable to protein. Then by deducting from the total oxygen consumption and carbon dioxide production, the oxygen and carbon dioxide attributable to protein, the *nonprotein respiratory quotient* can be found. Knowing the nonprotein quotient, the oxygen consumption, and the carbon dioxide production, the heat production attributable to the nonprotein foodstuffs can be calculated by reference to tables giving the caloric value of oxygen or of carbon dioxide per liter at different respiratory quotients. To this heat production is added that attributable to protein combustion. By further use of the table, the amount of carbohydrate and fat oxidized can easily be calculated.

In calorimetric studies the determination of the metabolism due to protein is often omitted, it being assumed that the metabolism is at the expense of only carbohydrate and fat. The error involved in this simplification is usually so small as to be of no consequence. The example given below will serve to illustrate the calculations of indirect calorimetry when the nitrogen metabolism is omitted. For further details of the method of calculation, and various modifications, reference may be made to the books by Lusk, Du Bois, and Peters and Van Slyke, and to the review by Richardson.

Analysis of the Oxidation of Mixtures of Carbohydrate and Fat

R.Q.	Percentage of Total Heat Produced by		Calories per Liter of O_2
	Carbohydrate	Fat	
0.70	0	100.0	4.686
0.71	1.10	98.9	4.690
0.72	4.76	95.2	4.702
0.73	8.40	91.6	4.714
0.74	12.0	88.0	4.727
0.75	15.6	84.4	4.739
0.76	19.2	80.8	4.751
0.77	22.8	77.2	4.764
0.78	26.3	73.7	4.776
0.79	29.9	70.1	4.788
0.80	33.4	66.6	4.801
0.81	36.9	63.1	4.813
0.82	40.3	59.7	4.825
0.83	43.8	56.2	4.838
0.84	47.2	52.8	4.850
0.85	50.7	49.3	4.862
0.86	54.1	45.9	4.875
0.87	57.5	42.5	4.887
0.88	60.8	39.2	4.899
0.89	64.2	35.8	4.911
0.90	67.5	32.5	4.924
0.91	70.8	29.2	4.936
0.92	74.1	25.9	4.948
0.93	77.4	22.6	4.961
0.94	80.7	19.3	4.973
0.95	84.0	16.0	4.985
0.96	87.2	12.8	4.998
0.97	90.4	9.58	5.010
0.98	93.6	6.37	5.022
0.99	96.8	3.18	5.035
1.00	100.0	0	5.047

(Data from Lusk.)

In four hours a fasting hen consumed 5.58 liters of O_2 and produced 3.97 liters of CO_2.

$$R.Q. = \frac{3.97}{5.58} = 0.71$$

Referring to the table on p. 448, it is seen that when the R.Q. is 0.71 a liter of oxygen has a caloric value of 4.69.

$$\text{Total heat production} = 5.58 \times 4.69 = 26.17 \text{ Cal.}$$

Referring again to the table, one sees that when the R.Q. is 0.71, the percentage of heat derived from carbohydrate is 1.10 and from fat 98.9.

$$\text{Calories from carbohydrate} = 0.011 \times 26.17 = 0.29$$
$$\text{Calories from fat} = 0.989 \times 26.17 = 25.88$$
$$\text{Grams of carbohydrate oxidized} = \frac{0.29}{4.1} = 0.07$$
$$\text{Grams of fat oxidized} = \frac{25.88}{9.3} = 2.78$$

In herbivores, especially ruminants, the respiratory quotient is influenced by carbon dioxide derived from fermentation in the alimentary canal (p. 212). Allowance must be made for this carbon dioxide in experiments involving a determination of the respiratory quotient in these animals when they are not in the postabsorptive state.

BASAL METABOLISM

The term basal metabolism, or basal metabolic rate, refers to the heat production of a resting animal in a thermally neutral environment and in the fasting or postabsorptive state, when the stimulating influence of food will have disappeared. In man and carnivorous animals the postabsorptive condition is reached 12 to 18 hours after the last meal. In herbivores, on the other hand, it is attained much later, because of the great mass of ingesta in the digestive tract. In steers Benedict and Ritzman found that a fairly uniform metabolic rate is reached 65 to 80 hours after food. This is in substantial agreement with Forbes, Fries, and Kriss, who observed that in cattle the bulk of the material in the alimentary canal at the beginning of a fast is eliminated in 2 to 3 days. In the hen a uniform rate of metabolism is usually evident 24 to 30 hours after the last food (Dukes). The methods used in basal metabolism determinations are those of animal calorimetry, either direct or indirect.

Normal Values. It is generally known that the basal metabolic rate per unit of body weight of small animals is greater than the rate per

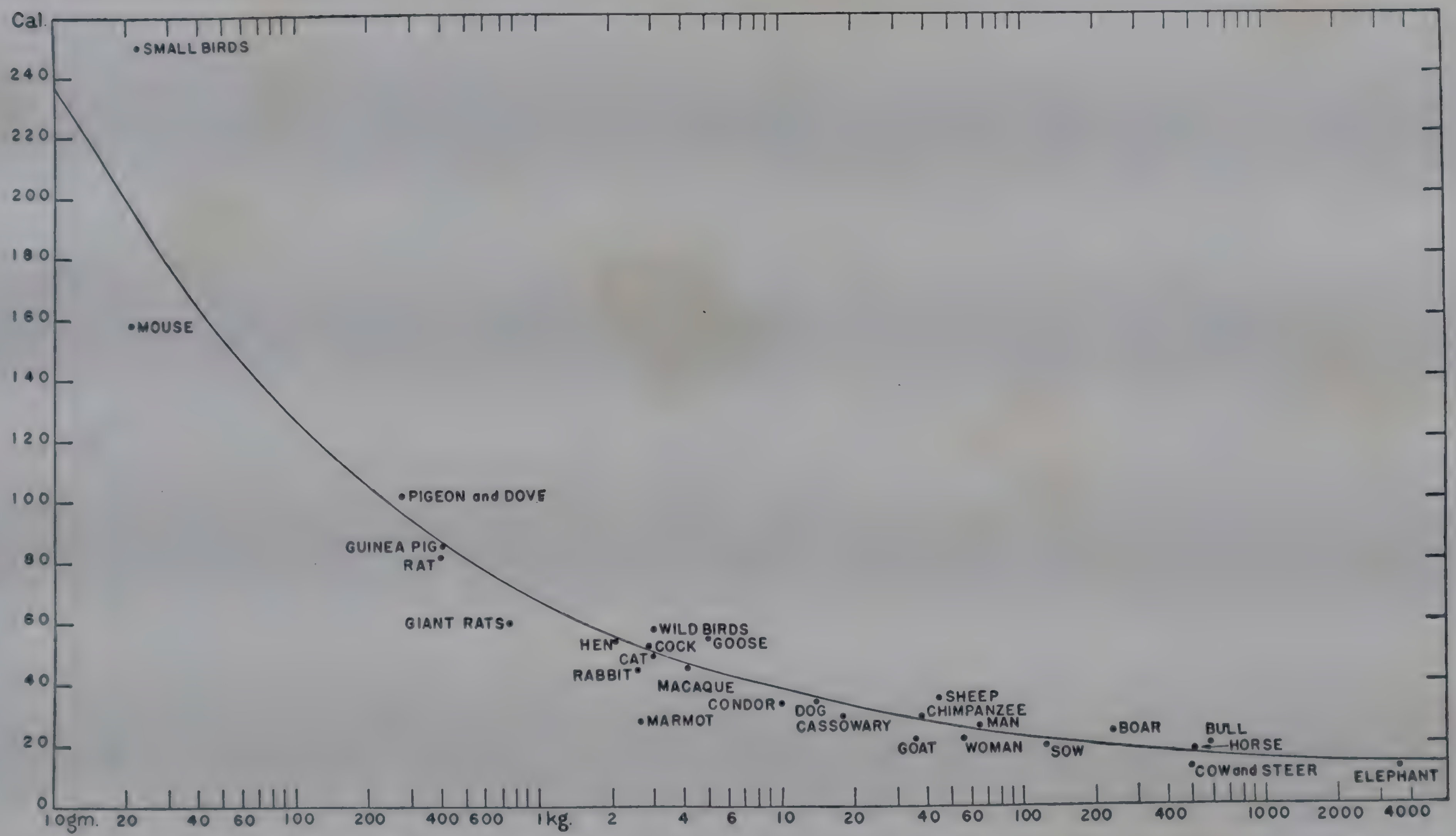

FIG. 106.—Relationship between average basal metabolic rate per kilogram per day of different species (vertical axis) and average body weight (abscissa). The weight range is from 20 gm. to 4000 kg. Semilogarithmic chart. (From Benedict, *Vital Energetics: A Study in Comparative Basal Metabolism*, Carnegie Institution of Washington Publ. No. 503, 1938.)

unit of body weight of large animals (Fig. 106). The surface area of small animals is greater in relation to the body weight than that of large animals. It has been widely believed that the higher metabolic rate of the small animal per unit of body weight is due to its larger surface. Heat is lost at the surface; the greater the surface, the greater is the heat loss and therefore the heat production. The relationship is sometimes regarded as causal. Furthermore, it has been widely believed that the basal metabolic rate per unit of body surface is practically constant in mature animals of all species (see Lusk).

The foregoing conceptions are usually generalized by saying that the basal metabolic rate of mature warm-blooded animals is proportional to the body surface area. This is the so-called *law of surface area*. It is equivalent to saying that basal metabolic rate and surface area bear a linear relationship to each other. Since the surface area of geometrically similar objects varies as the two-thirds power of their volumes (and weights, if the densities are the same), it is often said that basal metabolism is proportional to the two-thirds power of body weight.

However, it has been repeatedly pointed out by Benedict that there are many exceptions to the law of surface area. The deviations from the law are so numerous and so great, according to the work of this investigator, as to throw doubt on the validity of the generalization, particularly where causal relationship between surface area and basal metabolic rate is assumed. Fig. 107 shows the daily basal metabolic rates of animals of many species, and of greatly varying weights, when calculated per square meter of body surface area. Evidently the heat production per unit of surface area among different species is far from constant.

The surface area of an animal is estimated by the use of a formula, or indirectly in the living animal as by means of a surface integrator, or in the dead animal by removing the skin and determining its area after cutting it into pieces. Many formulas have been developed for estimating the body surface area of animals. Of these the formula of Meeh is one of the earliest and best known, and is as follows:

$$S = k \times W^{2/3}$$

where S is the surface in square meters, W the weight in kilograms, and k a constant for each animal. The value of k for different animals is shown in the table (Rubner, cited by Lusk). Benedict has suggested that k be assigned a value of 0.10 for all species.

Man	0.123
Dog	0.112-0.103
Calf	0.105
Sheep	0.121
Cat	0.099
Pig	0.087
Guinea pig	0.085
Fowl	0.104
Rat	0.091

Brody, on the basis of extensive studies of energy metabolism in farm animals, and a critical analysis of the work of others, sees little practical and no theoretical reason for referring the metabolism of animals to their surface areas. Furthermore, there is the important consideration that no sufficiently accurate method is available for determination of surface area. Brody found, for instance, that the exponent of the Meeh formula may vary from 0.32 to 0.72 in different animals. Other formulas may give errors of considerable magnitude

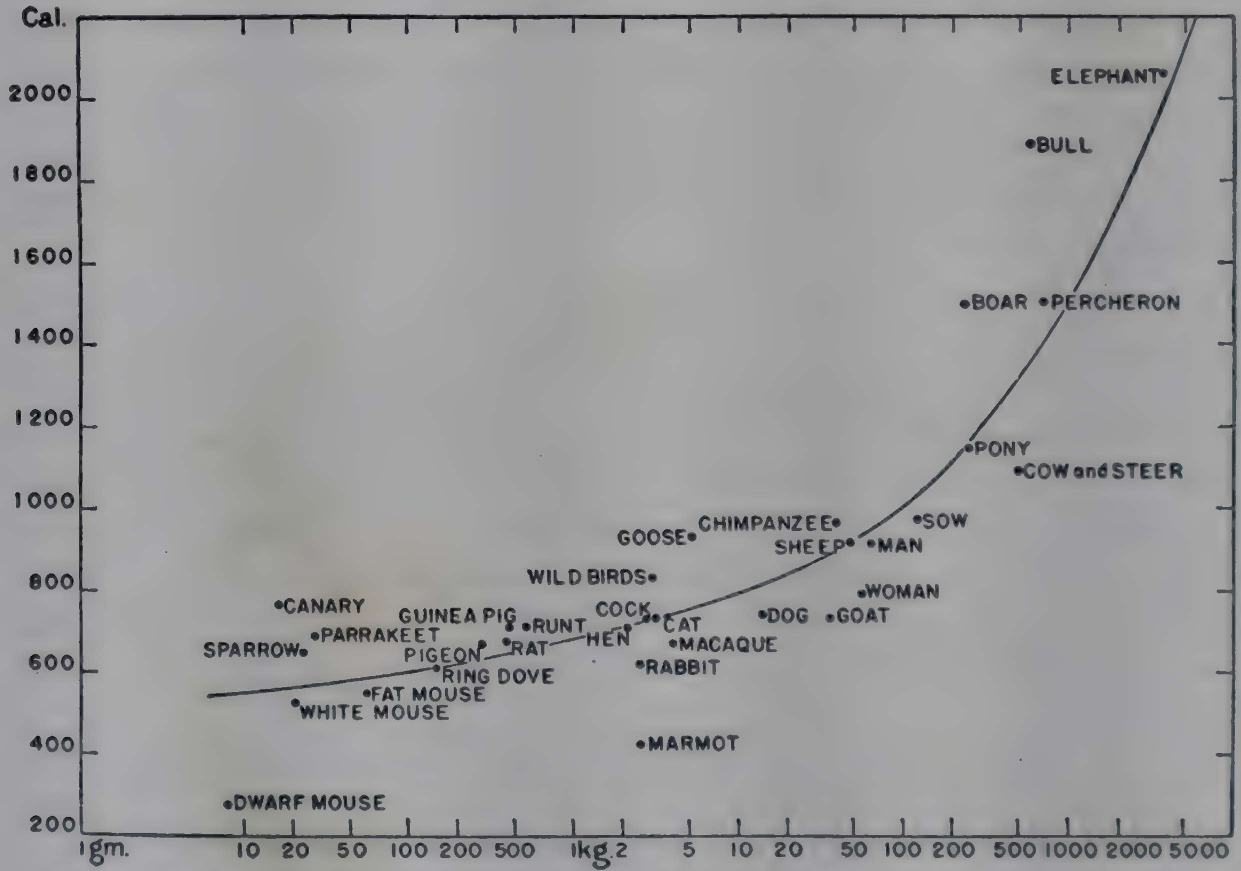

Fig. 107.—Relationship between average basal metabolic rate per square meter of surface area per day (vertical axis) and average body weight (abscissa) of many species. The weight range is from 8 gm. to 3700 kg. Semilogarithmic chart. (From Benedict, *Vital Energetics: A Study in Comparative Basal Metabolism*, Carnegie Institution of Washington Publ. No. 503, 1938.)

because of the difficulties met with in direct determinations of surface areas, on which measurements the formulas are based. Lacking a satisfactory method of determining surface area, Brody suggests that basal metabolism be referred to body weight raised to some power. For, after all, it is the body weight, and not the body surface, which one measures. The equation proposed by Brody for relating basal metabolism to body weight, for mature animals of all species, is

$$Q = 70.5M^{0.734}$$

in which Q represents Calories of heat produced per day and M the body weight in kilograms. When the data used in deriving the equation were represented graphically, it was found that practically all the points were within ± 20 per cent of the curve of the equation. For a recent comprehensive discussion of basal metabolism in relation to body weight, see Brody's book (Chapter XIII).

In spite of the objections raised by a number of investigators, it is still common practice in many laboratories to refer the metabolic rate of different species to a unit of body surface (square meter) or to a unit of body weight, or to each.

Lability. It has recently been emphasized by Ritzman and Benedict that the basal metabolism of dairy cattle is subject to great variability. This fact has not been fully appreciated in the past. Lability of basal metabolism is seen not only in different animals but in the individual animal. It is attributed, at least partially, to selective breeding, forced feeding, and variations in endocrine activity. Lability of metabolic rate, not so marked, has also been noted in the horse, sheep, and steer (Benedict and Ritzman) and the hen (Dukes).

FACTORS INFLUENCING THE METABOLIC RATE

Various factors influence the metabolic rate, among which may be mentioned food, muscular work, environmental temperature, and disease.

Food. It has long been known that there is an increase in heat production incident to and following the ingestion of food. This increase is spoken of as the specific dynamic effect. The term was originally applied to the stimulating effect of protein but has been extended to include the less pronounced effects of carbohydrate and fat. The process whereby the specific dynamic effect is brought about is termed the specific dynamic action. Not only do the individual foodstuffs exert a heating effect when ingested, but so does the mixed diet. The heating effect of the mixed diet may be quite different from the sum of the heating effects of the individual foodstuffs fed separately. It is desirable to have a separate expression to designate the total heating effect of the diet. Work of digestion, thermic energy, heat increment, and calorigenic effect are terms that have been proposed from time to time. In measuring the heat increment or calorigenic effect, the animal is brought into the postabsorptive state and its heat production determined. Then the foodstuff or the diet in question is fed and the heat production measured until it falls to the original postabsorptive level. The extra heat represents the specific dynamic effect or the heat increment of the meal.

The heat increment of feeding is largely wasted. In cold weather, however, it aids in warming the body, and during work a part of the specific dynamic effect of glucose can be used, as is noted below.

A large meal of meat may increase the metabolic rate of dogs as much as 90 per cent above the basal. The metabolic rate of dogs may be raised as much as 20 to 37 per cent above the basal by carbohydrate ingestion, and as much as 30 per cent by fat ingestion. The maximum heating effect of fat is seen at the sixth hour after ingestion (Lusk). In steers the metabolic rate may be increased nearly 50 per cent above the fasting level by the ingestion of 7 kg. of timothy hay and nearly 60 per cent by the ingestion of 7 kg. of alfalfa hay (Benedict and Ritzman). These are surprisingly high results especially as regards timothy hay, which is a protein-poor food. It is possible that the metabolic stimulus is due in part to lower fatty acids formed during the bacterial digestion of these foods rich in crude fiber.

The cause of the calorigenic effect of the food is not fully known. The extra peristalsis, secretion, and excretion necessitated by the ingestion and metabolism of the food are doubtless factors. Deamination and urea formation are believed to be important contributing causes in the specific dynamic action of protein. It was at one time thought that carbohydrates and fats increased heat production in accordance with the law of mass action; an increase in their concentrations in the internal environment would increase their utilization. Present evidence makes this view less probable. A thermodynamic interpretation is favored (Brody, 1945). Acid substances, for example, fatty acids, may have a stimulating effect on the cells.

Many reviews on the specific dynamic action are available (Lusk; Brody and Proctor; Wilhelmj; Mitchell and Hamilton, 1929; and others).

Work. Muscular activity increases the rate of metabolism. If no mechanical work is performed, all the increase of energy appears as heat, whereas if mechanical work is done only a part of the increase assumes the form of heat. The standing animal expends more energy than the lying, for increased muscular effort is required in standing. However, no mechanical work is done. Hall and Brody studied the energy increment of standing over lying in cattle and sheep and found that the average was about 9 per cent. A very fat steer showed an increment of 13 per cent. In the horse, however, the situation is different, the metabolic rate in this animal while standing being no greater than it is while lying (Brody, 1945). The anatomical arrangement of muscles, joints, tendons, and ligaments in the limbs of the horse are such that the limbs can be fixed in standing without extra heat production.

The efficiency of a machine, animate or inanimate, is the percentage of the total energy expended that can be converted into mechanical work.

$$\text{Efficiency} = \frac{\text{Work energy performed (Cal.)}}{\text{Energy expended (Cal.)}} \times 100.$$

The energy not realizable as mechanical work disappears as heat. The maximum efficiency of muscular work is of the order of 25 per cent. This applies to horses, both large and small, and to man. It appears therefore that efficiency is independent of animal size (Brody and Cunningham). The efficiency of several engines is approximately as follows: steam engines without condensers, 7.5 per cent; steam engines with condensers, 9 to 19 per cent; gas engines, 14 to 18 per cent; Diesel engines, 29 to 35 per cent; electric accumulator, 70 to 74 per cent (Brody and Cunningham).

It has been shown that the heat production due to the specific dynamic action of protein cannot replace the heat production due to mechanical work; there is a summation of the two heat increments. On the other hand, a part of the specific dynamic effect of glucose can be used for work (Lusk).

Environmental Temperature. An environmental temperature above or below certain points raises the heat production of the body. There is an environmental temperature at or below which the rate of metabolism of an animal must be increased to prevent a fall of body temperature. This environmental temperature, known in the resting, fasting animal as the *critical temperature*, shows great interspecific and considerable intraspecific variations. If the environmental temperature falls below the critical, heat production by the organism must increase if the body temperature is to remain constant. If the environmental temperature is raised above the critical, heat loss by radiation, convection, conduction, and the vaporization of water is increased so that the temperature of the body and the rate of metabolism are not materially increased. However, if the environmental temperature is further raised, there comes a time when the regulation against overheating is no longer able to prevent a rise of body temperature. The warming of the active protoplasm by the rise of body temperature causes an increase in the metabolic rate in accordance with the van't Hoff law (p. 546). Between the critical temperature and the temperature at which metabolism is increased because of warming of the protoplasm,[1] there is a *zone of thermal neutrality.* In this zone environmental temperature is without much effect on metabolic rate. In small animals the zone of thermal neutrality is narrower and at a higher temperature level than in larger animals.

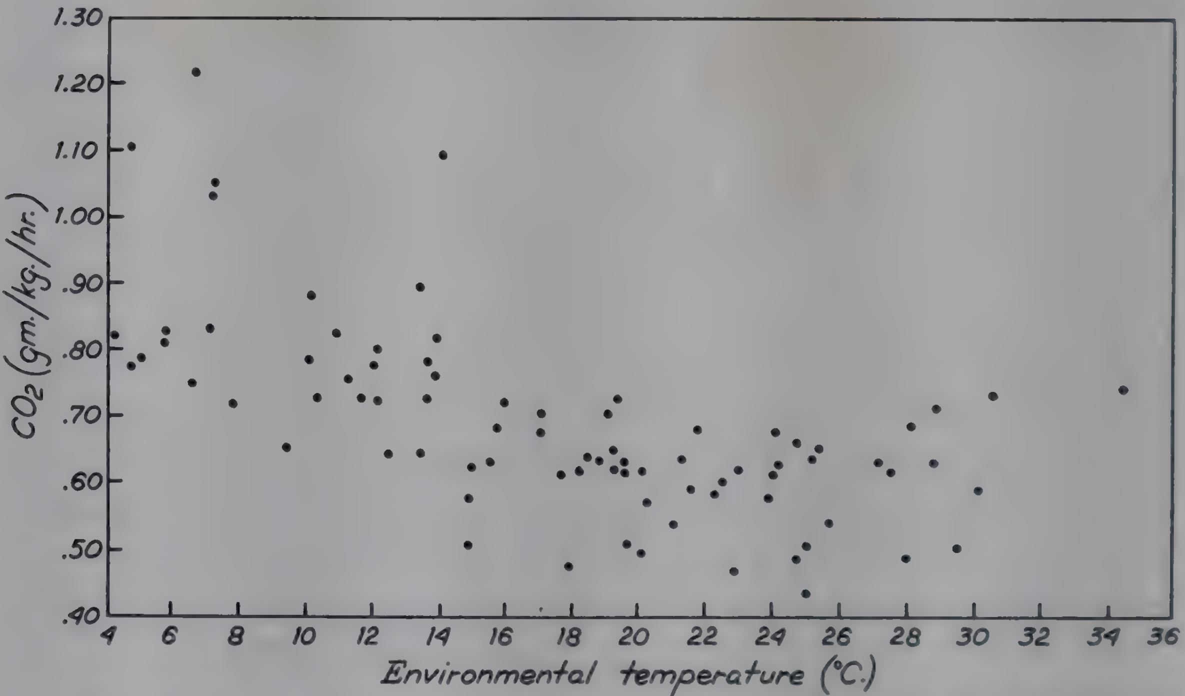

FIG. 108.—Effect of environmental temperature on the metabolic rate (carbon dioxide production) of fasting hens. The zone of thermal neutrality appears to lie between approximately 16 degrees C. and 26 degrees C. Below 16 degrees C. the metabolic rate tends to rise because of the cold. This is the critical temperature. Above 26 degrees C. there is a tendency for the metabolic rate to rise again, doubtless because of a rise of body temperature (see also p. 546). The duration of the fast in these experiments was long enough to insure a stable respiratory quotient. The carbon dioxide production is therefore a satisfactory index of metabolic rate.

In the hen Mitchell and Haines obtained an average critical temperature of approximately 16.5 degrees C. They cite results obtained by other investigators as follows: pig, 21 degrees C.; steer with closely sheared hair, greater than 18.3 degrees C.; steer with a full coat of hair, less than 15.5 degrees C.; dog before clipping, between 13.6 and 15.1 degrees C.; dog after clipping, between 23.8 and 26.5 degrees C. The zone of thermal neutrality in goats (fasting) extends from about 20 degrees C. to 28 degrees C. (Ritzman and Benedict). Data (unpublished) obtained by the author in a large number of experiments on fasting hens indicate that the zone of thermal neutrality extends from about 16 degrees C. to about 26 degrees C. In general, below an environmental temperature of 16 degrees C. and above one of 26 degrees C. the metabolic rate was increased (Fig. 108). A further discussion of the critical temperature is given in Chapter XXVII.

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[1] Traditionally, the lower limit of the zone of thermal neutrality is the critical temperature. Some writers, however, apply the term to the upper limit as well. In this sense there would be two critical temperatures—a lower, at which cold begins to affect the metabolic rate, and an upper, at which heat begins to be effective.

Disease. As regards man, Boothby and Sandiford state that "except in thyroid disorders and in leukemia there is very little variation from normal of the basal metabolic level." In conditions associated with hyperthyroidism there is a definite tendency for the basal metabo-

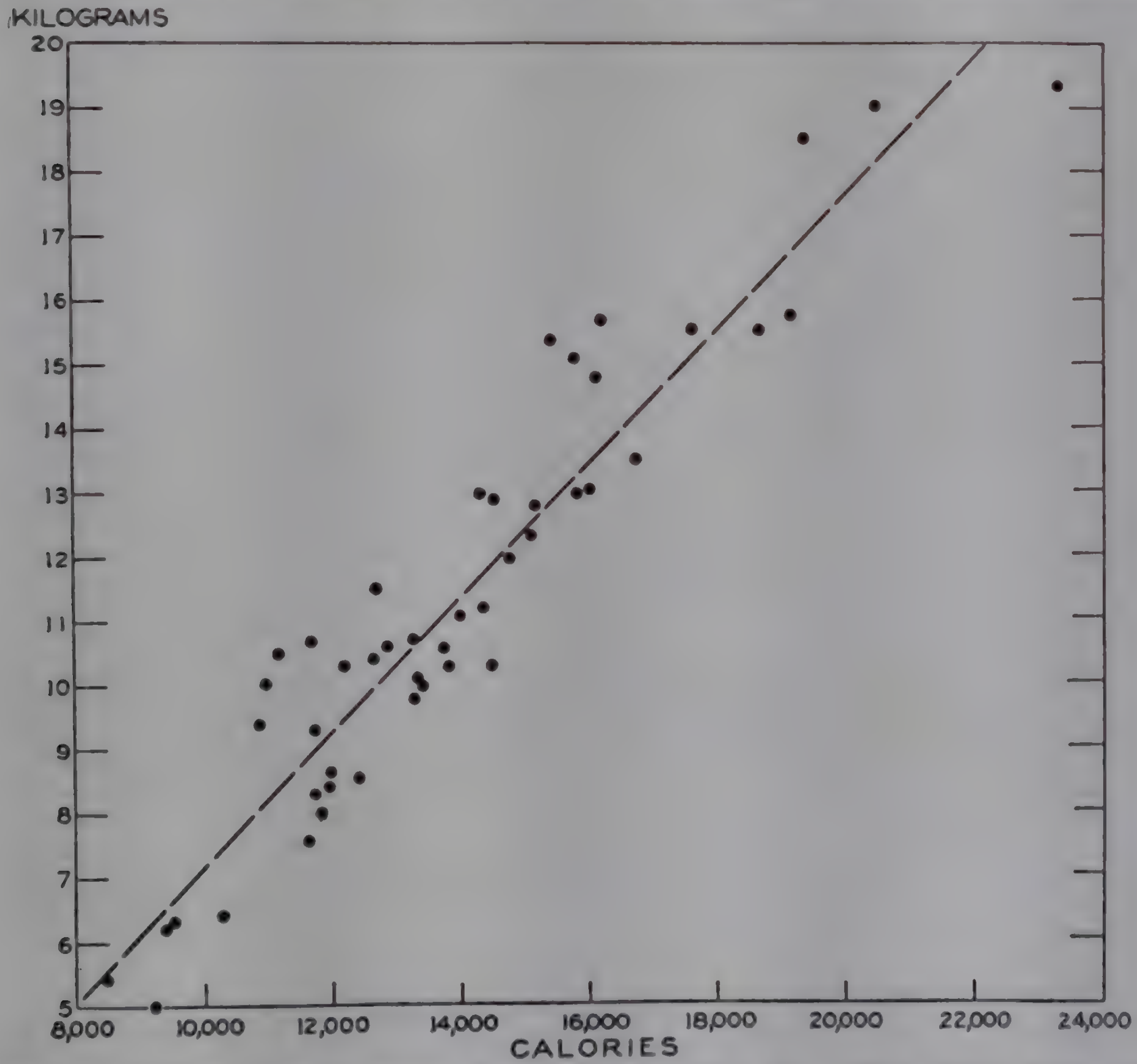

FIG. 109.—The relation between insensible loss of body weight (kilograms) and metabolic rate (calories) of cows on feed. The insensible loss and the heat production are on a 24-hour basis. The environmental temperature ranged between 18 and 22 degrees C. The cows were dry. (From Ritzman and Benedict, *Nutritional Physiology of the Adult Ruminant*, Carnegie Institution of Washington Publ. No. 494, 1938.)

lism to be elevated, while in conditions associated with hypothyroidism the opposite tendency prevails. In leukemia the basal metabolism is increased.

The effect of disease on the basal metabolic rate of animals has been little studied. Olson and Dukes studied the basal metabolic rate of chickens affected with fowl paralysis, transmissible fowl leukosis, and certain spontaneous neoplasms. The basal metabolic rate of birds affected with fowl paralysis was normal. Chickens affected with transmissible fowl leukosis had only a moderately elevated basal metabolism. Two cases of lymphocytoma were associated with a great increase of the basal metabolic rate. A case of myelocytoma and one of atypical lymphocytoma showed a considerable elevation of the basal metabolic rate. In fever the basal metabolic rate is increased in accordance with the van't Hoff law (p. 546).

THE RELATION BETWEEN INSENSIBLE LOSS AND METABOLIC RATE

The insensible loss in body weight of an animal is the weight of the gaseous outgo (CO_2, H_2O, and, in herbivorous animals, CH_4) minus the weight of the gaseous income (O_2). It has been shown in a number of species (man—Benedict and Root; cow—Kriss; Mitchell and Hamilton, 1936; Ritzman and Benedict; hen—Dukes; and others) that there is a positive correlation between the insensible loss and the metabolic rate. Most of the measurements have been made with the subjects under basal conditions. When the respiratory quotient is 0.723, the insensible loss is represented entirely by the water vaporized from the body, for then the weight of carbon dioxide eliminated is equal to the weight of oxygen consumed. It has been suggested that the insensible loss be used as a means of estimating basal metabolism.

The relation between insensible loss of body weight and metabolic rate of cows on feed is shown in Fig. 109.

Chapter XXIII

PROTEIN METABOLISM[1]

IN THE alimentary canal the proteins of the foods are hydrolyzed to amino acids, in which form they are absorbed into the portal blood. In this way they reach the liver, where their metabolism begins. (It is probable however, that some protein absorption occurs in the form of peptides.) A large portion of the amino acids, however, passes through the liver and enters the general circulation by which they are transported to the tissues generally, where they undergo metabolic changes. The blood always contains amino acids. Some are of dietary origin; others are derived from the body proteins. In an adult mammal in nitrogen equilibrium, synthesis of tissue protein must be accompanied by an equivalent degradation of body protein; the amino acids so formed are presumably returned to the blood. From this pool the amino acids are distributed to the various tissues, the liver as well being supplied with these in proportion to the blood flow through it. The metabolism of amino acids in the liver continues, in lesser degree, even during the nonabsorptive periods. A study of protein metabolism thus resolves itself essentially into a study of the metabolism of the amino acids. (In this book the significance of the purines, allantoin, creatine, and creatinine is treated in Chapter XX; the nitrogen balance, in Chapter XXII.)

One of the following fates awaits amino acids absorbed from the alimentary tract: (1) deamination (deaminization) with the formation of urea from the amino group, the carbon-hydrogen residue (α-keto acid) subsequently being oxidized, reaminated, or converted into carbohydrate; (2) synthesis into living protein; (3) utilization for some specific purpose, such as the formation of hormones, bile salts, pigments, and catalysts.

THE USE OF ISOTOPES IN THE STUDY OF THE INTERMEDIARY METABOLISM OF PROTEIN

A new method of attack on the problem of the intermediary metabolism—the building up, interconversion, and tearing down of organic molecules in the organism—has been used in recent years. It involves the use of isotopes of the elements that make up organic compounds: C, H, N, S, O.

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[1] Dr. J. A. Dye contributed very largely to the revision of this chapter.

In biological studies two types of isotopes are available, the naturally occurring stable isotopes of hydrogen, oxygen, nitrogen, carbon, and sulfur, all of which are now available, and the artificially produced radioactive isotopes, a great number of which have been prepared. Isotopes of the same elements have practically identical chemical properties and are indistinguishable by the living protoplasm. Isotopes of the same elements are therefore treated alike by the cells. Organic compounds whose only differences are those occurring in their isotopic content are also treated alike by the cells.

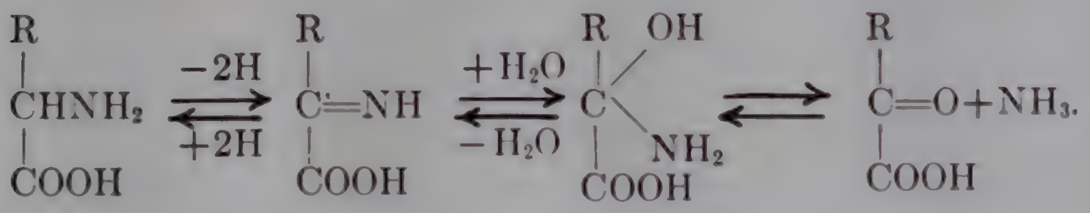
In the study of the intermediary metabolism of protein, isotopic nitrogen is used to mark the amino groups, while deuterium (heavy hydrogen) or isotopic carbon may be used to mark the carbon chain. The isotopic compound is administered to the animal, and then various organs or their constituents are examined for the isotope.

A rather extensive literature now exists covering studies of intermediary metabolism made by the use of isotopic tracers. This work not only verifies much of the earlier work in many respects, but sheds new light on certain fundamental physiological processes which could be obtained only by the use of these or similar methods. The additional information obtained by these studies is rapidly being incorporated into our conceptual knowledge concerning intermediary metabolism, with the result that previously poorly understood physiological processes are now being clarified (Schoenheimer and Rittenberg, Schoenheimer).

DEAMINATION AND UREA FORMATION

Within the course of a few hours following the ingestion of protein, the time varying in the different species, a quantity of nitrogen approximately equivalent to that in the absorbed amino acids is excreted in the urine. This must be so if the animal is in nitrogen equilibrium. Primarily because of this fact it was assumed, until recently, that the greater portion of the absorbed amino acids is deaminated immediately by the liver before gaining entrance into the general circulation. This portion may appropriately be termed the exogenous amino acid metabolism since the amino acids undergoing this fate do not enter into the substance of the tissue protein. This concept, however, neglects the important fact that the tissues are also sources of blood amino acids, which upon passing through the liver may also be deaminated. The process of synthesis and degradation of tissue protein, together with the ultimate deamination of the amino acids or any other fate which they undergo, may appropriately be termed endogenous amino acid (protein) metabolism. By the use of tracer technics it appears that the larger portion (approximately two-thirds) of the dietary amino acids is used in the latter manner in the animal body. The amino acids of the blood and tissue fluids, regardless of whether they arise immediately from the diet or from the tissue proteins, may be considered as a metabolic pool of amino acids from which the tissues, including the liver, may obtain amino acids. Recent evidence further indicates that these various metabolic processes are going on continuously; that is, the tissue proteins are no longer to be considered as static structures, but dynamic ones which are in a state of flux with the amino acids of the tissue fluids and blood, the amino acids absorbed from the alimentary canal, and those that are a part of the plasma proteins. Syntheses, degradations, deamination, reamination, and transamination are the processes involved in this "dynamic state of body constituents" (Schoenheimer).

Deamination, the process of removing the NH_2 group from the amino acids, has been demonstrated to occur in the liver, kidney, and muscles; it probably occurs in other tissues as well. The present evidence indicates that deamination is brought about by oxidation or by both oxidation and hydrolysis. It is usually represented as follows:

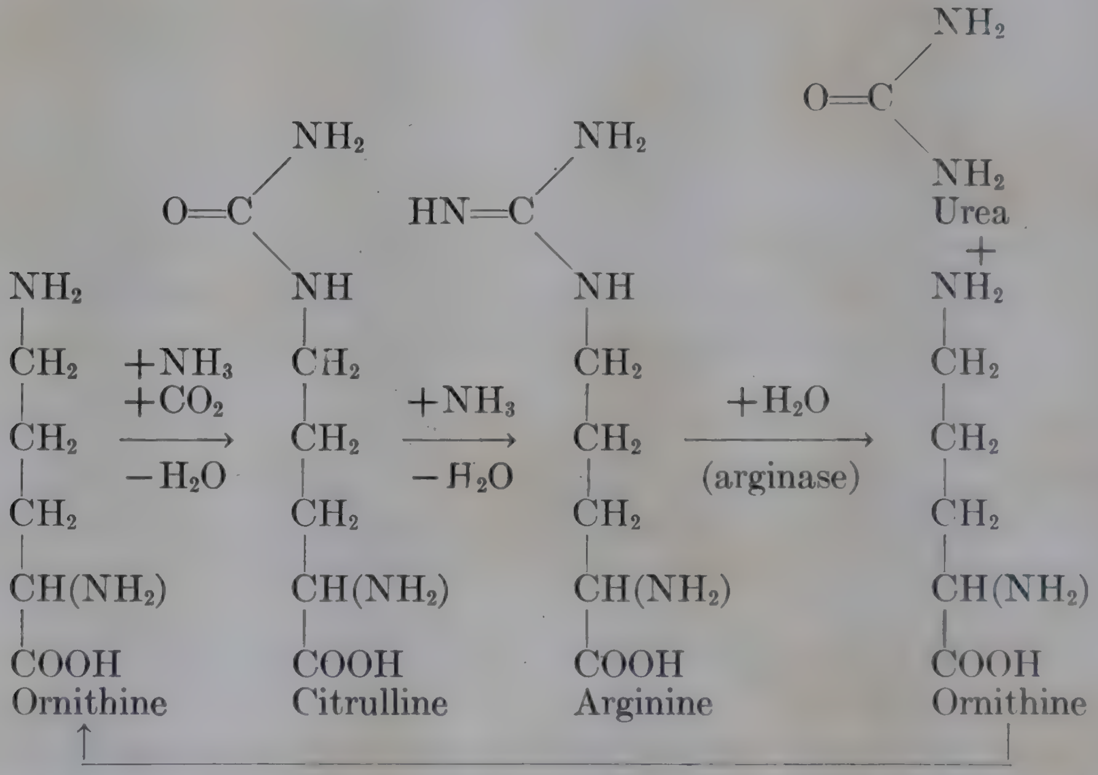


$$\begin{array}{c} R \\ | \\ CHNH_2 \\ | \\ COOH \end{array} \underset{+2H}{\overset{-2H}{\rightleftharpoons}} \begin{array}{c} R \\ | \\ C{=}NH \\ | \\ COOH \end{array} \underset{-H_2O}{\overset{+H_2O}{\rightleftharpoons}} \begin{array}{c} R \quad OH \\ |\diagup \\ C \diagdown \\ | \quad NH_2 \\ COOH \end{array} \rightleftharpoons \begin{array}{c} R \\ | \\ C{=}O + NH_3. \\ | \\ COOH \end{array}$$

α-Amino acid α-Imino acid Hydrated imino acid α-Keto acid

The amino acid is first oxidized by the removal of hydrogen into an α-imino acid; the latter is then hydrated and ultimately split into ammonia and an α-keto acid. The process is reversible and the enzyme systems involved have been described. By this reaction the amino group of a given amino acid may be used to aminate the α-keto acid of another amino acid. This is one process by which transamination may occur. Similarly transamination may occur in the extrahepatic tissues.

The next topic relates to the formation of urea from the ammonia split off in the process of deamination. Urea is the principal form in which mammals excrete nitrogen from the body. Most of the urea arises from the deamination of amino acids. Just what the steps are in the formation of urea is not fully known. A theory that was at one time widely accepted is that the ammonia derived from deamination is converted to a carbonate, which is dehydrated to a carbamate, which in turn is dehydrated to urea. Although it is generally agreed that the liver can form urea from ammonium salts, the present evidence indicates that the relatively simple theory just outlined is inadequate to explain the process. A more recent theory of urea formation which has wide acceptance is that of Krebs and Henseleit. According to this theory ammonia and carbon dioxide unite with the amino acid ornithine to form citrulline, which reacts with ammonia to form arginine. This is then hydrolyzed by the enzyme arginase to ornithine and urea. Ornithine is used over and over again catalytically in the production of more arginine. The urea formed in the reactions is excreted. Following are the essential reactions:



As noted on p. 418, the evidence indicates that the liver is the sole seat of urea formation in all mammals. The conversion of arginine to ornithine by the liver enzyme arginase is the reaction that is limited to the liver. The other reactions can occur in other tissues.

THE FATE OF THE NONNITROGENOUS PART

One of four possible fates awaits the nonnitrogenous fractions of amino acids following deamination. (1) All amino acids apparently yield fractions that may be oxidized to carbon dioxide and water. (2) Some amino acids yield fractions that may be converted into sugar. (3) Some amino acids yield fractions that may give rise to the ketone substances. (4) α-Keto acids may be reaminated and serve as tissue builders.

Sugar from Amino Acids. Not all amino acids are capable, after deamination, of yielding sugar in the body, although many possess this power. The following ones have been shown by Lusk and his co-workers, Dakin, and others to be potential glucose formers: glycine, alanine, serine, cystine, aspartic acid, glutamic acid, hydroxyglutamic acid, arginine, proline, and oxyproline. More recent work adds histidine and valine to the list.

The usual method of determining whether an amino acid or other substance is a sugar former is to feed the substance to a fasting animal made diabetic by injection of the glucoside phlorhizin, by the injection of alloxan, or by pancreatectomy. In phlorhizin diabetes the renal threshold for glucose is lowered to the extent that glycosuria and hypoglycemia result, whereas in pancreatic diabetes the ability of the animal to utilize glucose is diminished and glucose appears in the urine in large amounts. After several days of fasting in these animals the carbohydrate reserves become practically exhausted, but glucose continues to be eliminated in the urine. This glucose must come from noncarbohydrate sources and it is believed that protein is the chief source. If the ratio glucose/nitrogen (G/N or D/N ratio) in the urine is known, it is possible to calculate the amount of glucose derived from the catabolism of body protein. According to Lusk, the D/N ratio of the fasting phlorhizin-diabetic animal is 3.65:1. From this it is evident that the catabolism of 100 gm. of body protein would give rise to 58 gm. of glucose in the diabetic organism ($3.65 \times 16 = 58.4$).[1]

If known amounts of mixtures of proteins or individual proteins are fed to the fasting diabetic animal, the glucose and the nitrogen eliminations are increased. From this extra glucose and extra nitrogen the glucose-forming power of the protein fed may be determined. When meat is fed, the D/N ratio remains at 3.65:1, but some individual proteins give higher values and some lower. This is because of differences in their content of amino acids, some of which are glucogenic and some not. By feeding the individual amino acids, the glucogenic power of each may be determined.

Another way of determining whether an amino acid or other substance is a glucose former is to feed it to an animal whose liver has been freed of glycogen (as by fasting or muscular exercise). After a suitable time the liver is examined for glycogen. It is assumed that any glycogen found was derived from the substance fed.

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[1] A D/N ratio of 3.65:1 has not been obtained by all workers on this problem. Therefore there is some difference of opinion as to the percentage of glucose derived from protein.

For the formation of fat from protein (amino acids), see p. 474.

Ketones from Amino Acids. As will be shown later, fatty acids may, in the course of their catabolism, yield fragments known as ketone substances. Similarly, the nonnitrogenous fragments of some of the amino acids may give rise to these substances. Histidine, phenylalanine, tyrosine, and leucine are the amino acids that may behave in this way. To determine whether an amino acid is a ketone former it is perfused through the surviving liver or is fed to a diabetic animal. Amino acids are not an important source of the ketones.

INDISPENSABLE AND DISPENSABLE AMINO ACIDS

Of the 23 primary amino acids, 10 have been shown to be indispensable components of the diet, whereas 13 have been shown to be dispensable. Outstanding progress in this field of inquiry has come in recent years, largely as a result of the work of Rose and collaborators. By feeding various mixtures of purified amino acids as the sole source of nitrogen, together with adequate amounts of carbohydrates, fats, inorganic salts, and vitamins, these investigators have determined which of the amino acids are dietary essentials and which are not. The usual procedure was to omit one or two of the amino acids from the diet at a time. Young rats were the experimental animals.

Rose defines an *indispensable amino acid* as one that cannot be synthesized by the body, out of the materials ordinarily available, at a rate sufficiently rapid to promote normal growth. A *dispensable amino acid* is one that can be synthesized in sufficient quantity out of materials ordinarily available to the organism.

Following is the classification of amino acids with respect to their growth effects (Rose).

Indispensable Amino Acids

- Lysine
- Tryptophane
- Histidine
- Phenylalanine
- Leucine
- Isoleucine
- Threonine
- Methionine
- Valine
- Arginine

Dispensable Amino Acids

- Glycine
- Alanine
- Serine
- Norleucine
- Aspartic acid
- Glutamic acid
- Hydroxyglutamic acid
- Proline
- Hydroxyproline
- Citrulline
- Tyrosine
- Cystine

Arginine is not necessary for slow growth, but it is required for normal growth. Hence, according to the foregoing definition, it is an indispensable amino acid.

Work on the problem of indispensable and dispensable amino acids is being extended to other species. Rose and Rice have reported results for the dog. Qualitatively the amino acid requirements of the dog are the same as those of the rat. For the adult dog arginine is not an essential dietary constituent.

Almquist (1942, 1945) and Almquist and co-workers have studied the amino acid requirements of the chick. These investigations show that the number of essential amino acids for the chick may be greater than for the mammal. The following additional ones are dietary essentials under certain conditions: cystine, glutamic acid, glycine, proline, and tyrosine.

A recently discovered amino acid is hydroxylysine. It is not a dietary essential.

Why Certain Amino Acids are Dietary Essentials. In considerations having to do with the dispensability or indispensability of amino acids, it should be kept in mind that in the metabolic processes all amino acids are required by the organism. A large number of them can, however, be synthesized by the body if other amino acids are available in sufficient quantity and kind. These are, therefore, from the standpoint of the diet nonessential. The indispensable amino acids possess some group or have some structural arrangement that is required in the metabolic processes and that cannot be formed in the body from other substances. These amino acids are therefore required in the diet. Aside from being necessary for the formation of protein, the essential amino acids play special roles in metabolism. These have been discussed by Peters and Van Slyke. Methionine is concerned in transmethylation, that is, the donation of labile methyl groups for the formation of such compounds as choline and creatine. Phenylalanine or tyrosine is the source of the benzene ring required for the formation of a number of biologically important compounds, for example, adrenaline and thyroxine. The body cannot synthesize this ring. Tyrosine is not a dietary essential, for it can be synthesized from phenylalanine. However, the latter is an indispensable amino acid. Tryptophane is believed to owe its indispensability to the presence in its molecule of the indole ring. Histidine possesses the imidazole ring, which the body cannot synthesize. Therein lies the explanation of its essential nature. Arginine is concerned in the formation of urea and it is the source of the amidine group used in the formation of creatine. Lysine can undergo deamination but the process is irreversible. Therein lies the explanation of its indispensability. Once it is deaminated, it is beyond recall. The reasons for the indispensability of leucine, isoleucine, threonine, and valine have not been determined.

THE SYNTHESIS OF PROTEIN IN THE RUMEN

Bacterial action in the rumen plays an important part in cellulose digestion (p. 326) and vitamin synthesis (p. 527) in ruminants. It has been demonstrated that bacterial action is also of significance in protein synthesis in the rumen. Recent work has given ample confirmation to the old view that the nitrogen of amides such as urea and of ammonium salts may be utilized by ruminants as a partial substitute for dietary protein. The utilization is made possible by the action of bacteria in the rumen which synthesize amino acids from nonprotein nitrogenous substances and build the amino acids into their own protoplasm. Farther along the alimentary tract the bacteria are digested and yield amino acids that are absorbed by the host. As much as one-third of the protein requirement of ruminants can be met by the use of urea in the diet. During the recent war, when there was a widespread shortage of protein, urea was commonly used in dairy rations. Because of protein synthesis in the rumen, it is evident that the amino acid content, that is, the protein quality, of the diet is less important in ruminants than in other animals.

The number of bacteria in the rumen that are capable of synthesizing urea into their own protein must be very great. Experiments indicate that organisms from rumen contents diluted 100 billion times are able to carry out this synthesis (Gall).

THE QUALITY OF PROTEIN

The quality or nutritive value of the different proteins is not the same. Of the protein that is absorbed, a certain amount is wasted in the metabolic processes. The lower the quality of the protein the greater is this wastage. The explanation of differences in protein quality lies in the fact that the various amino acids that cannot be built by the body are found in varying proportions in the different proteins. Evidently those proteins that contain amino acids of such kinds and in such proportions as are required for nutritive purposes possess the greatest nutritive value. The term *biological value* has been introduced to designate the value of a protein for purposes of maintenance and growth. It is a numerical expression, and may be defined as the percentage of the absorbed nitrogen that the body retains or fails to excrete in the urine.

$$\text{Biological value} = \frac{\text{N retained}}{\text{N absorbed}} \times 100.$$

The following figures show the biological value of the proteins of various foods for maintenance and growth of rats (Mitchell): hen's egg, 93; milk, 85; pork muscle, 74; rice bran, 68; wheat, 67; potato, 67; cottonseed, 66; oats, 65; soybean, 64; alfalfa hay, 62; corn, 60; coconut, 58; navy bean, 38. From these results it appears that, in general, the biological values of proteins are somewhat higher for maintenance than for growth and maintenance, and that with a few exceptions biological values do not differ very greatly. Working with pigs, Mitchell and Kick obtained biological values as follows: for the proteins of corn, 54; for the proteins of tankage, 42; for the proteins of a combination of corn and tankage, 61. Proteins containing different amino acids supplement each other.

Studies on the efficiency of the protein in different rations for growing lambs have been made by Miller and Morrison. The estimated biological values of the proteins, as revealed by this work, did not differ greatly from one another. Following are the rations and the biological values: corn and alfalfa hay, 59; corn and a mixture of alfalfa hay and timothy hay, 60; corn, a mixture of alfalfa hay and timothy hay, and soybean-oil meal, 64; and corn, timothy hay, and soybean-oil meal, 62. The similarity of these biological values is explainable in terms of protein synthesis in the rumen. In practical nutrition the quality of protein for ruminants is less of a problem than for omnivores and carnivores. Results obtained in studies of biological values of proteins on rats or pigs are not applicable to ruminants.

THE QUANTITY OF PROTEIN

Assuming that the protein is of the right quality, the question arises as to the minimum and optimum amounts necessary to meet the needs of the body.

If protein is completely withdrawn from the diet and a large amount of fuel in the form of carbohydrate and fat is fed, the nitrogen excretion falls to its lowest level. This is known as the minimum protein catabolism and represents an unavoidable loss in the metabolic processes. If protein is now added to the diet it will be found that nitrogen equilibrium cannot be established simply by giving an amount of protein equivalent to the minimum protein catabolism. About three times the latter are required. This is the minimum subsistence-requirement of protein, or the physiological protein minimum. In order to maintain nitrogen equilibrium at this low level, it is essential that sufficient calories, in the form of carbohydrate and fat, be fed to meet the energy requirements of the animal. It might be supposed that the minimum amount of protein necessary to maintain nitrogen equilibrium would be the same as the hygienic protein requirement, or the smallest protein intake consistent with health. Nutrition studies and practical experience show, however, that it is necessary to feed more than the physiological protein minimum if health is to be maintained. In the average adult human being the hygienic minimum is greater than 35 gm. per day but how much greater is not definitely known. "The standard quite generally accepted to provide the necessary margin of safety is 1 gram of protein per kilo per day" (Peters and Van Slyke).

In mature warm-blooded animals of many species, ranging in size from mice to cattle, Brody, Proctor, and Ashworth have shown that the endogenous (minimum) urinary nitrogen tends to increase with the 0.72 power of body weight. This relationship is shown by the equation

$$N = 146\ M^{0.72}$$

in which N is the endogenous urinary nitrogen excretion in milligrams per day and M the body weight in kilograms. They recommended tentatively that the maintenance requirement of digestible crude protein for all animals be placed at four times the protein equivalent ($N \times 6.25$) of the endogenous nitrogen excretion in the urine. The calculated values are found to agree very well with standard feeding practices.

EFFECT OF MUSCULAR WORK ON PROTEIN METABOLISM

That amino acids, following deamination, may be oxidized in the body is undoubted. Probably the chief form in which combustion occurs is as sugar, some 58 per cent of the protein molecule being convertible to this substance. Under ordinary conditions, however, most of the energy needed by the body is derived not from protein but from carbohydrate and fat. A question which has aroused much interest is whether or not muscular work increases the metabolism of protein. Since the body possesses little power of storing protein, apart from incorporating it in the living tissue, and is therefore during muscular work unable to call upon a nonliving reserve of protein comparable to the carbohydrate and fat reserves, the question resolves itself essentially into whether muscular work causes an increased breaking down of the living tissue (mainly muscle). From a careful consideration of the literature, Lusk was led to conclude that muscular work entails no greater output of nitrogen in the urine than does rest, which is to say that muscular work causes no increase in the protein metabolism. Cathcart, on the other hand, concluded from the evidence that muscular work does increase the metabolism of protein as indicated by the nitrogen content of the urine. He believes, however, that the increase is small. The question is reviewed also by Mitchell and Hamilton (1929), who conclude that "it appears that an increased breakdown of body tissue is not an *inevitable* consequence of muscular work, but that it may occur, even though the diet is sufficient in energy." In the new knowledge of protein metabolism, work is not regarded as increasing the output of nitrogen in the urine.

PROTEIN NUTRITION BY INTRAVENOUS INJECTION

It is possible to maintain an animal in nitrogen equilibrium by the intravenous injection of compatible plasma, hydrolyzed protein, or pure amino acids. As in ordinary feeding, it is necessary that all the essential amino acids be present in the material injected. Otherwise nitrogen equilibrium cannot be maintained. A number of recent studies in this field have been made and the findings have added considerably to our basic knowledge of protein metabolism. Furthermore the method is being used clinically on human patients unable to take nourishment by mouth, and there is reason to think that it will find application in veterinary medicine. The general subject is reviewed by Elman.

Chapter XXIV

FAT METABOLISM[1]

THE commonly accepted view regarding fat digestion and absorption (p. 386) is that the food fats are, in the alimentary canal, hydrolyzed by lipase into fatty acids and glycerol, and that in this form, and possibly to some extent in the form of soaps, they are absorbed. In the mucosa of the intestine these absorbed products are converted again to neutral fats. During fat absorption an increased phospholipid metabolism has been demonstrated to occur in the intestinal mucosa (p. 386). This has led to the belief that phospholipids act as intermediary products in the synthesis of fatty acids to neutral fat (Sinclair). Some of the phospholipid itself appears in the lymph. The chief medium for the removal of the fat from the wall of the intestine is the lymph.

According to the partition hypothesis of fat absorption (p. 387), some of the fat in the intestine is absorbed in unhydrolyzed form as a fine emulsion of particles less than 0.5 micron in diameter. This fat goes to the systemic circulation via the lymph system. Another portion is absorbed as fatty acids via the portal circulation. This theory of fat absorption is discussed in a recent review by Frazer and is compared with the more commonly accepted lipolytic hypothesis.

FAT TRANSPORT

A fundamental difficulty which confronts the animal organism in the transport and final metabolism of fats is the insolubility of neutral fats or their constituent fatty acids in water, blood, and tissue fluid. The body uses several methods to overcome this obstacle. The hydrotropic bile salts are instrumental in effecting the absorption of fatty acids. In the intestinal villi neutral fats enter the lymph system, to a large extent at least, in the form of a fine emulsion. The particles, or *chylomicrons*, are composed of neutral fat and are 0.5 to 1 micron in diameter; they are readily visible under the dark-field microscope (Gage and Fish). The same kind of fat particles are found in the blood stream. Following a meal containing fat, the blood chylomicron count rises from the postabsorptive level to a maximum, the magnitude of which depends upon the quantity of fat being absorbed, and then falls again to the postabsorptive level. In addition to the chylomicrons, there is the possibility that fat particles smaller than 0.5 micron in diameter exist in the blood.

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[1] Dr. J, A. Dye contributed very largely to the revision of this chapter.

The decrease in the blood fat is due to one or more of the following processes: (1) decrease in the quantity of fat being absorbed; (2) storage as depot fat; (3) phosphorylation of fat, or conversion of neutral fat to phospholipids; (4) formation of cholesterol esters; and (5) utilization of fat by the tissues for energy purposes. Lecithin and cholesterol esters, in addition to neutral fat, must be regarded as important compounds in the transport of fatty acids. Both the phospholipids and the cholesterol esters are more water-soluble than either neutral fats or fatty acids. The problem of solubility is referred to again in the discussion on the production and utilization of the ketone bodies (p. 479). By the use of radioactive phosphorus as an indicator and by other means, it has been shown that the chief places of phospholipid formation are the intestinal tract, the liver, and the kidney. From these places of its formation, particularly the liver, phospholipid is carried to the other tissues for utilization.

The fat metabolism of lactating cows and goats has been extensively studies by Maynard and co-workers (Maynard and McCay, Bender and Maynard, Williams and Maynard). These investigations indicate that the blood lipid concentration is markedly influenced by changes in the amount of the fat intake, the changes being in general in the same direction. The maximum changes in the concentration of the blood lipids, however, did not occur immediately after the changes in the amount of the fat intake, which were sudden; a good many days elapsed before the blood changes became fully effective. It was also shown that a strong parallelism exists between the total lipids, the phospholipids, and the cholesterol of the blood; thus a close metabolic relationships among these substances seems evident (Fig. 110). The changes involve chiefly the plasma lipids. The lipids of the blood cells tend to remain constant. Changes in the blood lipid level following changes of short duration in the fat intake (single feedings) are more sharply defined in carnivorous animals than in herbivorous. In other words, *alimentary hyperlipemia* is not easily induced in herbivores.

The passage of Fat between Blood and Tissues. There are two views concerning the form in which fat is transported from the blood to the tissues. One is that the chylomicrons, and possibly finer fat particles, referred to above, pass through the walls of the capillaries and enter the tissues with little or no change. The other view is that fat is transported from the blood to the tissues largely in the form of the phospholipid lecithin. It is probable that both methods are employed in the body. Particulate fat entering the tissues probably represents fat on the way to the fat depots. The phospholipids entering the tissues may represent lipid that is to be oxidized by the tissues, built into protoplasm, or stored.

Fat in the fat depots can enter the blood for transportation. It probably does so in the form of neutral fat. However, from the organs in which phospholipid is formed (intestine, liver, kidney) there must be a considerable passage of phospholipid into the blood.

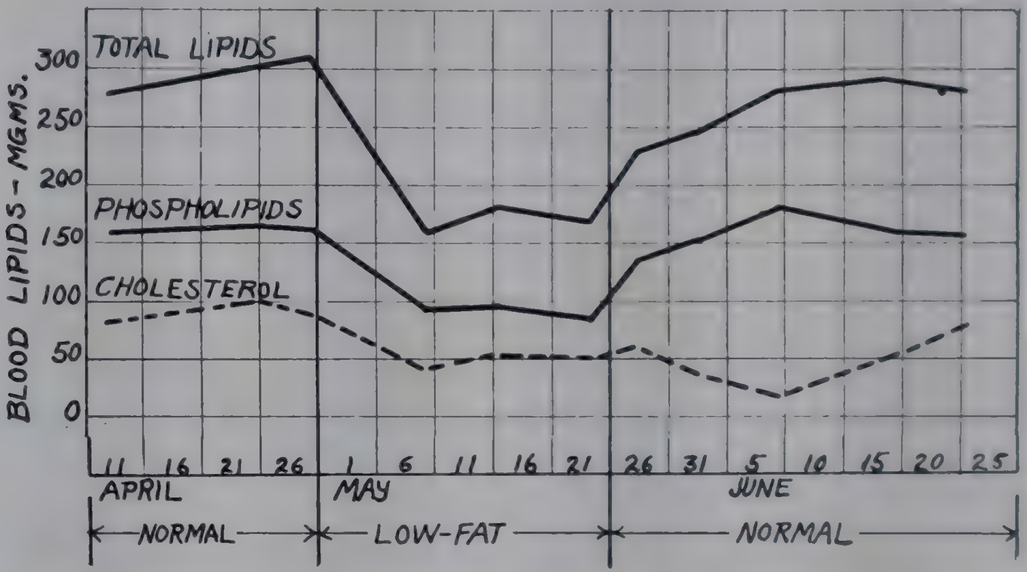

FIG. 110.—The relationship between the blood lipids and the diet in a goat. Note the parallelism that usually exists between the total lipids, phospholipids, and cholesterol. The nature of the diet is indicated at the bottom of the graph. (Adapted from Bender and Maynard, *Journal of Dairy Science,* 1932, 15.)

STORED FAT AND TISSUE FAT

Fatty material (lipid) exists in the tissues in at least two forms: storage fat, and tissue fat or that fat which appears to be an integral part of protoplasm.

Storage or depot fat may occur in many tissues of the body, but the most important locations are the subcutaneous connective tissue, the intermuscular connective tissue, and the abdominal cavity. This fat consists chiefly of the glycerides of palmitic, stearic, and oleic acids. It originates from absorbed food fat, which is deposited rapidly and extensively, and from the conversion of dietary carbohydrates and proteins to fat. It represents a reserve supply of material that may be mobilized for oxidation by the tissues to meet the energy needs of the organism. The amount of the storage fat varies greatly depending upon the nutritive state of the animal, the species, and other factors. Because it is quantitatively variable, it is sometimes referred to as the *variable element.* During fasting, when the carbohydrate reserves are quickly reduced to a low level, there is an increase in carbohydrate synthesis from noncarbohydrate substances (gluconeogenesis) and an increased metabolism of depot fat to meet the energy needs of the organism. Studies of the respiratory quotient show that this is true. In chickens, for instance, a quotient indicating essentially fat combustion is usually reached 24 to 30 hours after the last feeding.

Each animal ordinarily stores a fat that is largely characteristic of the species. Yet when a foreign fat is fed in large quantities, it may be deposited with little or no change. It is a well-known fact that certain foods when fed to animals have a tendency to cause the formation and deposition of a soft fat. In swine feeding, peanuts, soybeans, and mast are the common foods that produce soft pork. These foods are rich in unsaturated fats. A store of soft fat may be converted into one of hard fat by feeding for a time a diet high in carbohydrates, which lead to the deposition of a hard fat.

From the work of Bloor and of Schoenheimer, it seems evident that the foregoing changes in fats are explainable in terms of one or more of the following: (1) changes brought about during absorption, such as rearrangement of the fatty-acid assortment that is combined with glycerol; (2) the selective oxidation of fats or fatty acids which are not characteristic of the species; (3) the mixing of absorbed fat with fat derived from carbohydrate; and (4) the continuous transport of depot fat to the liver, which by conversion of one fatty acid to another produces an assortment of fatty acids characteristic of the species. The last factor is presumably very important and is considered again on p. 477.

Tissue fat is that portion of the fat, or lipid, of the body which cannot be detected with the microscope, cannot be stained with the ordinary fat stains, and cannot be extracted by the usual fat solvents. The best-known constituents of tissue fat are the phospholipids lecithin, cephalin, and sphingomyelin. Because the tissue lipids were believed to be relatively constant in kind and amount under practically all physiological conditions, they were designated as the *constant element.* The belief in the constancy of the tissue lipids as to amount has been confirmed by more recent work, but that the fatty acids of the phospholipids may change qualitatively has also been shown.

Tissue phospholipids are probably a part of the protoplasm, much as are protein, inorganic salts, and water. By reason of the unsaturated bonds of their fatty acids, they may be able to acquire oxygen and later to release it to the oxidative mechanisms of the cells. This would mean that they are concerned in cell respiration. The phospholipids of the tissues may, to some extent, represent intermediary products in the metabolism of fat.

The physiology of the phospholipids is reviewed by Sinclair and by Bloor.

FORMATION OF FAT FROM CARBOHYDRATE AND PROTEIN

That the fat of the food, when present in amounts beyond the immediate needs of the body, may be stored as fat is a well-recognized fact. The possibility of fat formation from carbohydrate and protein may now be considered.

Formation from Carbohydrate. It has been known since the time of Lawes and Gilbert that animals may convert carbohydrate into fat. Numerous subsequent experiments and practical experience in feeding farm animals bear this out. Some of the experimental evidence hinges around the fact that an animal on a carbohydrate-rich diet may, in a given time, lay down in its body more fat than was consumed in the food or could be accounted for on the basis of the transformation of protein. Other evidence is derived from studies of carbon and nitrogen balances and of the respiratory quotient (Chapter XXII).

It has been shown that there is failure of synthesis of fat from carbohydrates when thiamine is lacking in the diet. The action of thiamine in this respect appears to be mainly that of increasing the food intake. Riboflavin and pantothenic acid probably have a similar effect. The composition of the synthesized fat is characteristic of the species. The exact mechanism of the synthesis of fat from dietary carbohydrate is unknown. It is improbable that it is a direct condensation of hexose molecules. A more likely mechanism is one involving phosphate intermediaries with the aid of enzyme systems. In the conversion of oxygen-rich carbohydrates to oxygen-poor fats the respiratory quotient may be greater than unity because of the extra oxygen derived from the former. Thus after giving starch to a pig Wierzuchowski and Ling found that quotients of about 1.4 were maintained for many hours. Evidence is accumulating from various sources that the liver is an important, if not the principal, site of conversion of carbohydrates to fats. Other tissues, however, may subserve this function.

Formation from Protein. It is known that certain amino acids may yield sugar in the body and that sugar may be converted into fat. Hence it should be possible for protein to serve as a source of fat, and experiments make it practically certain that it can (Lusk, Bloor). However, it is difficult to demonstrate the transformation of protein into fat, and it is doubtful if under ordinary conditions of feeding the amount of the change is of any importance. The following facts help to explain why the formation of fat from protein in the body is slight: (1) the amount of protein in the diet is comparatively small; (2) only some 58 per cent of the protein molecule is glucogenic and probably only a part of this glucose is converted to fat; (3) fat is less easily oxidized in the body than carbohydrate.

Lusk reports experiments showing the formation of fat from protein. The glycogen stores of a dog were filled by carbohydrate feeding in the evening and a very heavy feeding of meat in the morning. During the height of the protein assimilation, studies of the respiratory quotient and the heat elimination indicated the deposition of fat. When the glycogen deposits were low, glycogen was formed. When the glycogen depots were moderately filled, and an excess of meat was fed, studies of the respiratory quotient indicated the deposition of both carbohydrate and fat, both derived from protein. Direct evidence of the formation of fatty acids from protein has been obtained by Longenecker and other workers.

LIVER FAT AND LIPOTROPIC FACTORS

Deficiencies of pyridoxine and thiamine are associated with a decreased fat synthesis and a decreased fat content of the liver. An excess of the same vitamins apparently augments fat synthesis and tends to produce fatty livers, especially if there is a concurrent choline deficiency. Choline administration under these conditions will prevent the development of fatty livers, phospholipid production will be increased, and more depot fat will be laid down.

Choline is a *lipotropic factor*, that is, it is capable of preventing the development of certain forms of fatty livers or of effecting the removal of fat from fatty livers. Methionine, betaine, and ethanolamine are also lipotropic since they play a part in the synthesis of choline in vivo. However, the animal body may be unable to synthesize enough choline to meet its requirements for this substance. Choline, or a choline precursor, may therefore be required in the diet. For this reason choline is usually classed as a vitamin (p. 531). Evidence has been presented that manganese has a lipotropic action, which is much greater when the choline content of the diet is low. Thus some interaction between manganese and choline is apparent (Amdur, Norris, and Heuser).

Under normal conditions the quantity of fat in the liver is fairly constant; an accumulation of excess fat in this organ is indicative of an alternation in fat metabolism. The production of fatty liver is generally due either to a failure of fat transport from the liver or to an increased mobilization of fat from the depots at such a rate that the liver is unable to handle it. Thus the fatty-acid content of the liver depends upon the following processes, all of which may be presumed to be proceeding concurrently in the normal animal: (1) the metabolic changes taking place in the varying amounts of dietary fatty acids reaching the liver; (2) the synthesis of fat from carbohydrates and proteins; (3) the metabolic changes brought about in fats transported from the fat depots to the liver, either at the normal rate of transport or at an accelerated rate (active mobilization); (4) phosphorylation of fats by the liver and the transport of these to the fat depots and tissues; and (5) degradation of fats, or fatty-acid oxidation, for energy purposes. An imbalance in one or more of these processes may increase or decrease the fat content of both the liver and the fat depots.

Another lipotropic factor is lipocaic (Dragstedt and co-workers). This substance, possibly a hormone, is produced by the pancreas, but it is not the same as insulin. For a time it appeared that lipocaic might be closely related to the pancreatic enzymes or might occur in the external secretion of the pancreas. Both of these possibilities seem to have been answered in the negative. Furthermore, the ideas that lipocaic owed its action to lecithin, choline, or betaine, or that the general lipotropic action of protein had been mistakenly attributed to lipocaic, have apparently been excluded by experimental work. The conclusion seems justified that lipocaic is a specific lipotropic factor produced by the pancreas. As noted above, it may be a hormone. It has not yet been obtained in pure form. How it prevents, or causes the disappearance of, an accumulation of fat in the liver is largely unknown. It is evident that it is in some way concerned with the transport and utilization of fat. In the absence of lipocaic, fat accumulates in the liver, probably because of an increased rate of mobilization of fat or a decreased ability of the liver to metabolize it. Still another lipotropic factor is inositol (p. 532). The lipotropic factors have been reviewed by McHenry and Patterson.

THE DYNAMIC STATE OF BODY FATS

Until recently depot fat was generally regarded as a physiological energy store which in animals in nutritional equilibrium was essentially stable both in quality and quantity, and was mobilized for energy purposes only in time of need. This viewpoint can no longer be supported owing primarily to the results obtained from experiments in which isotropic tracers were employed (Schoenheimer and other investigators). Most of this work has involved the use of fatty acids in which heavy hydrogen (deuterium) was stably bound to the carbon chain. A number of important advances in intermediary fat metabolism have been made by this method.

In an experiment in which palmitic acid, labeled with deuterium, was fed to normal rats which were in nutritional equilibrium, the isotope content of the body fat at the end of 8 days indicated that 44 per cent of the dietary fat had been deposited in the fat depots. Since the body weights of these animals remained constant, an equal quantity of depot fat must have been metabolized. Storage fat, like body protein, exists in a state of dynamic equilibrium with absorbed fat, blood fat, and liver fat. Depot fat is thus in a state of rapid flux. Schoenheimer estimated that 50 per cent of the body fat is turned over (degraded and regenerated) in 5 to 9 days; for liver fat alone the time is less than one day.

An analysis of the body fat for specific fatty acids following the feeding of palmitic acid which was stably tagged with deuterium revealed some unexpected results. In spite of the fact that only isotopically labeled palmitic acid was fed, deuterium was found attached to stearic, oleic, palmitoleic, myristic, and lauric acids in the storage fat. After feeding labeled oleic acid, similar results were obtained. Fatty acids containing more than one double bond, such as linoleic, linolenic, and arachidonic, were not formed. These results indicate the simultaneous occurrence of several physiological reactions for the explanation of which the following conclusions seem necessary: (1) the fatty-acid chain can be shortened or lengthened stepwise two carbon atoms at a time; (2) fatty acids can be desaturated to the extent of one double bond, for instance, the conversion of stearic to oleic acid; (3) unsaturated fatty acids can be saturated by hydrogenation with the removal of the double bonds; (4) desaturation to the extent of more than one double bond cannot be effected in the animal body. This last conclusion is of considerable importance, since Burr and co-workers have shown that linoleic, linolenic, and arachidonic acids (with 2, 3, and 4 double bonds respectively) are indispensable dietary requirements for rats.

It is evident, therefore, that the animal body is capable of converting one fatty acid into another and does so even when the fatty acids so formed are plentiful in the diet. These changes are continuous processes with little or no relation to the body requirements. The conversions are reversible. It seems quite unlikely that these processes take place in the fat depots; evidence is rapidly accumulating that the liver plays the primary role in these interconversions.

Body phospholipid and cholesterol are similarly in a state of dynamic equilibrium and rapid flux; the half time of the former is about 30 days, that of the latter about 20 days. The phospholipid turnover in the liver is extremely rapid, that in the tissues is slow.

SUMMARY OF LIVER FUNCTIONS IN RESPECT TO FAT METABOLISM

It may be helpful at this time to summarize the functions of the liver relative to the intermediary metabolism of fat. The following are regarded as normal functions:

1. Synthesis of fatty acids from carbohydrates.
2. Synthesis of fatty acids from proteins or amino acids.
3. Phosphorylation of fats: production of phospholipids from neutral fats.
4. Conversion of one fatty acid into another: interconversion of fatty acids.
    a. By stepwise removal of two carbon atoms at a time: ß-oxidation of fatty acids.
    b. By lengthening of the fatty-acid chain by the addition of two carbon atoms at a time.
    c. By desaturation of saturated fatty acids to the extent of one double bond.
    d. By saturation of unsaturated fatty acids by hydrogenation and removal of the double bonds.
5. Partial oxidation of fatty acids and the production of ketone bodies and lower fatty acids. This process is considered further under fat mobilization and oxidation.

FAT MOBILIZATION AND ITS OXIDATION

Besides the dynamic state or rapid flux of body lipids, the depot fats can be mobilized physiologically at more rapid rates if the body requirements so demand. The present evidence suggests that a hormone, or hormonal influence, of the anterior pituitary plays a special role in this process (Stetten and Salcedo). Injection of excess amounts of anterior pituitary extract leads to the production of lipemia, fatty liver, and a decrease in storage fat. Other factors may also be important in this process. When fat catabolism is accelerated, fat is transported to the liver in increased quantities presumably for processing in one way or another to render it more available to the tissues. Although some fat may be used directly by certain extrahepatic structures, a large part is first transported to the liver for processing. One of these liver activities is presumably the conversion of neutral fat to phospholipid; another is the production of acetic acid and the ketone bodies.

At the beginning of this chapter it was pointed out that an essential step in fat metabolism is the making of the fatty acids water-soluble. Prior to oxidation the neutral fats must undergo cleavage to fatty acids and glycerol. The latter substance, which constitutes approximately 10 per cent of the fat molecule, is believed to behave in fat metabolism like carbohydrate; it is glycogenic. That it may yield sugar to the body is indicated by the fact that when it is fed to animals (dogs) made diabetic by phlorhizin the sugar output in the urine is raised.

Although the higher fatty acids are insoluble in water, there is a good deal of evidence that they are oxidized by tissues such as skeletal and cardiac muscles for energy purposes. The evidence, however, is indirect and is derived mainly from studies of the respiratory quotient. The lower fatty acids, namely, acetic, butyric, caproic, caprylic, and to a lesser extent capric, are water-soluble and have been shown to be oxidized directly by the extrahepatic tissues, following hepatectomy in dogs, to the extent of about 50 per cent of the amounts oxidized in the intact normal animal (Dye and Marsters). The higher fatty acids are not only water-insoluble, but their sodium salts are toxic if present in the blood in any appreciable quantity. It now seems definitely established that to overcome these difficulties the fatty acids are normally partially oxidized in the liver to acetic acid and the ketone bodies, acetoacetic and β-hydroxybutyric acids. These are readily and rapidly oxidized by the extrahepatic tissues.

Relative to the ketone bodies, the following facts seem to be widely accepted: (1) the liver is the primary if not the sole site of ketone-body production; (2) ketone bodies are normal intermediary products in the metabolism of fatty acids and are normally present in the blood in small quantities; (3) ketone bodies are readily and rapidly oxidized by the extrahepatic tissues and supply energy for work, heat, and other purposes; (4) ketonemia and ketonuria arise only when the production of ketone bodies is in excess of their utilization; (5) in diabetes 10 per cent or less of the ketone bodies produced is excreted in the urine; (6) in diabetes the utilization of these substances is unimpaired (Chaikoff and Soskin, Dye and Chidsey); (7) there is no obligatory relationship between the oxidation of carbohydrates and fats as was previously believed (Dye and Chidsey), that is, the earlier idea that fats burned in the flame of the carbohydrates is no longer tenable; (8) although ketone bodies, especially acetoacetic acid, are toxic when present in excessive amounts in the body fluids, they are less toxic than the salts of the higher fatty acids (Dye and Chidsey).

The ketone bodies are not further oxidized or utilized by the liver which produces them. They are, however, readily oxidized by the muscles, heart, lungs, kidneys, and adrenal glands. Physical exercise increases the utilization of ketone bodies by muscles up to 10 times in normal animals and 3 to 5 times in diabetic animals.

Substances from which the liver can produce ketone bodies are (1) fatty acids with an even number of carbon atoms; (2) certain amino acids (p. 464); (3) fatty acids with 5 to 11 (odd-numbered) carbon atoms; and (4) possibly pyruvate. With the exception of fatty acids with an even number of carbon atoms, the production of ketone bodies from these substances is apparently quantitatively insignificant normally.

Our concepts concerning the physiological role of the ketone bodies in intermediary metabolism have changed materially in the last 20 years. The original classical theory of ketone-body production can no longer be accepted. This theory postulated a stepwise ß-oxidation of the fatty-acid chain up to the stage of butyric acid, which was only partially oxidized to acetoacetic acid in the absence of a simultaneous oxidation of carbohydrate (Knoop, Shaffer). A number of experimental results showed that this theory was untenable. The trend of thought then turned to the so-called multiple alternate oxidation theory. This postulates that the intact fatty-acid chain is oxidized at the ß-carbon and at each alternate carbon atom, with complete oxidative splitting of the acid into blocks of four carbon atoms each. In this manner four molecules of acetoacetic acid could be formed from palmitic acid. At the present time the most widely accepted theory of ketone-body formation is that of MacKay. It is known as the ß-oxidation-condensation hypothesis. According to this the fatty-acid molecule is split stepwise into acetic acid, two molecules of the latter being condensed to form acetoacetic acid. This process is normally very rapid. ß-Hydroxybutyric acid is produced in turn by the liver and other tissues by the reduction of acetoacetic acid. An appreciable portion of the acetic acid formed as just indicated probably passes into the blood as such to be utilized directly by the tissues. This idea would account for the observation of numerous workers that the theoretically possible maximal production of ketone bodies has never been obtained experimentally (Dye and Babcock). Some still believe, however, that no one theory of ketone-body formation accounts for all the experimental facts.

KETOSIS IN RUMINANTS

Cows and ewes often show ketosis during pregnancy and lactation. Ketosis of cows is sometimes designated as acetonemia; of ewes pregnancy disease. These disorders are characterized by ketonemia, ketonuria, and hypoglycemia. Acidosis may be present, for two of the ketone bodies are acids and to the extent that they are eliminated in the urine they will remove fixed base from the body. The metabolic disturbance that leads to an abnormal production of the ketones is apparently induced by insufficient consumption (1) of carbohydrate in easily available form or (2) of foods that yield carbohydrate in the body (Sampson and Boley, 1941; Sampson and Hayden; Roderick, Harshfield, and Hawn; Fraser and co-workers). Presumably the ketosis of ruminants results from an accelerated fat metabolism, which leads to an overproduction of the ketone substances. The augmented fat metabolism probably represents an effort of the body to meet its energy needs under conditions of a shortage of carbohydrate in the metabolic mixture. Present evidence indicates that the ketosis of ruminants is not associated with diabetes. In other words, there appears to be no decrease in the ability to oxidize glucose. It is a matter of glucose shortage.

The relationship between food intake, blood sugar level, and ketonemia in pregnant ewes is shown in Fig. 111. The inverse relationship

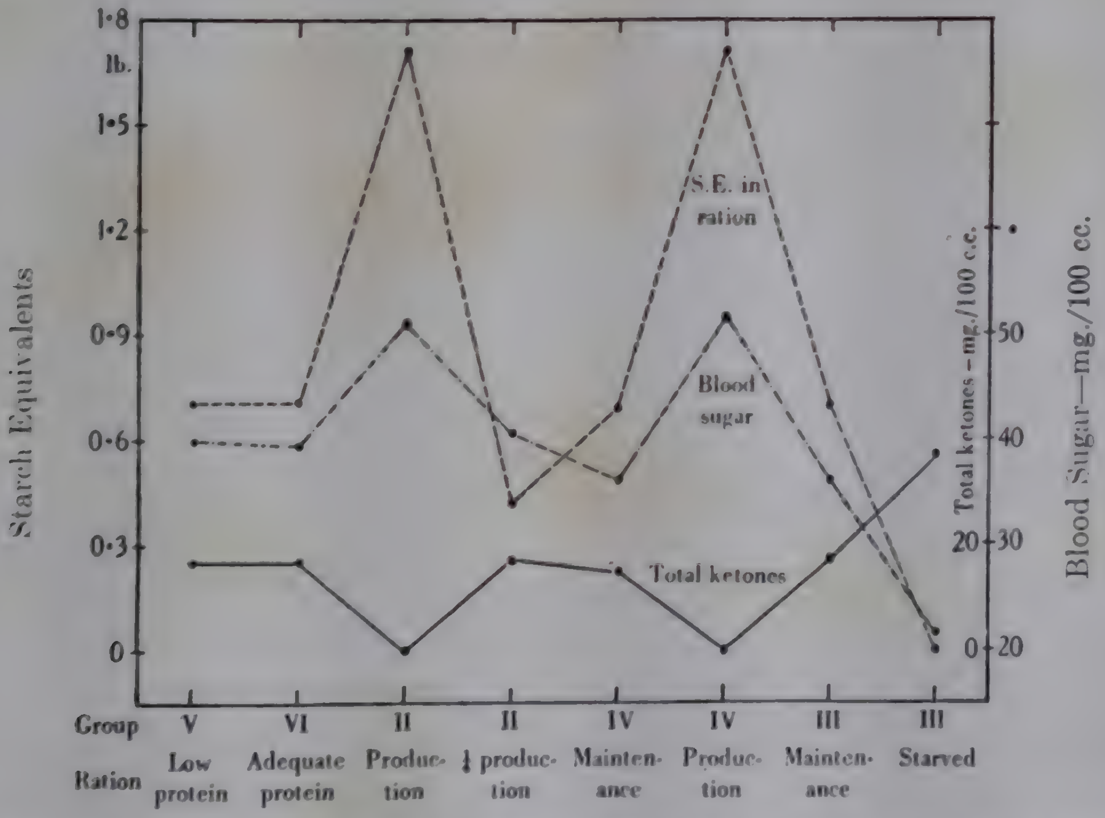

FIG. 111.—Relationship between food intake, blood sugar level, and blood ketone level in pregnant ewes. Each group consisted of 15 ewes. Note the inverse relationship between the caloric intake and blood sugar level on the one hand, and the ketonemia in these ewes. S.E., starch equivalents. (From Fraser, Godden, Snook, and Thomson, *Journal of Physiology*, 1938, **94**.)

between (1) the caloric intake and the blood sugar level and (2) the ketonemia is clearly evident.

From the physiological standpoint the soundest therapy in ketosis in ruminants would be the administration of glucose or similar carbohydrate. There is ample clinical and experimental evidence to support this point of view.

It has been suggested on meager evidence that deficiencies of thiamine or vitamin A might be related to the development of ketosis and that therefore these vitamins might be useful in the treatment of this condition. There is now a fair body of evidence in the literature that fails to show any relationship between ketosis and vitamins.

Chapter XXV

CARBOHYDRATE METABOLISM[1]

IN THE alimentary canal starch and the common sugars are hydrolyzed to the monosaccharides glucose, fructose, and galactose, in which forms they can be absorbed into the portal blood and transported to the liver. Cellulose and the other constituents of crude fiber, and the pentosans, all of importance in the diet of herbivorous animals, are, to the extent that they are digested, probably converted, by bacterial fermentation in the alimentary canal, to glucose and fatty acids of the lower series. Of the latter, acetic, propionic, and butyric acids appear to predominate in herbivorous animals, the first named being most abundant (p. 327). Should ruminants derive the major portion of their energy requirements from these lower fatty acids, sugar as such would probably play a secondary role in their metabolism (Marston, 1939). Of the lower fatty acids listed above, propionic and butyric are glycogenic while acetic and butyric are ketogenic; the necessary conversions occur mainly if not entirely in the liver. In addition to the monosaccharides absorbed as such and the glucose synthesized from the lower fatty acids, a large portion (as much as 58 per cent) of the absorbed amino acids and a small portion (the glycerol, about 10 per cent) of the absorbed fat can be converted into sugar by the liver. Generally speaking, two-thirds or more of the energy expended by the animal ultimately comes from the oxidation of carbohydrate, the available supply being represented by the glycogen present in the liver, muscles, and other tissues, and the glucose present at all times in the blood and tissue fluids.

GLYCOGEN

The metabolism of carbohydrate may be said to start with the formation of glycogen. It is therefore necessary to learn some of the biochemical and physiological properties of this important compound. Glycogen, a colloidal polysaccharide, was discovered in the liver, by Claude Bernard near the middle of the last century. Because it resembles starch in appearance and in some of its properties, it is sometimes spoken of as animal starch. It is whitish in color and soluble in water, the solution having an opalescent appearance. When tested with iodine solution it gives a port-wine color. Upon hydrolysis by acid, or one of the amylases together with maltase, glucose is formed.

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[1] This chapter was revised and to a large extent rewritten by Dr. J. A. Dye.

Occurrence. Glycogen is present in the liver of all animals, in which organ the greatest concentration is found. Its presence may be demonstrated both chemically and histologically. It is deposited in large amounts in the cytoplasm of the hepatic cells, although it has been observed in the intercellular capillaries, in the Kupffer cells, and even in the large venules. Under usual conditions the liver of the rabbit contains 5 to 7 per cent of glycogen and that of the dog 3 or 4 per cent. After heavy carbohydrate feeding as much as 12 per cent may be present. It is estimated that the liver of a rabbit of average weight may contain as much as 8 to 10 grams of glycogen and that of a man 150 grams (Macleod). The liver of the normal ewe (pregnant) contains, on the average, 3.8 per cent of glycogen (Roderick, Harshfield, and Merchant). When large amounts of glucose are given intravenously to dogs it has been found that the liver may store as much as 20 per cent of glycogen. This represents approximately its maximum glycogen-storing capacity (Butsch).

The occurrence of glycogen is by no means limited to the liver. It is found to some extent in practically all tissues. In dogs that had been liberally fed with carbohydrate shortly before killing, the following average percentage distribution of glycogen was found: muscle, 44.23; liver, 37.97; bone, 9.25; skin, 4.49; viscera, 3.81; heart, 0.17; brain, 0.09; blood, 0.015. From these figures and other studies it is apparent that the old view that one-half the glycogen is found in the liver and one-half in the rest of the body is incorrect.

The total content of carbohydrate in the bodies of young dogs has been shown to be equivalent to 4 to 5 gm. of glucose per kilogram of body weight. This includes glycogen, glucose, lactic acid, and possibly other intermediary substances of carbohydrate metabolism (Dye, unpublished).

Origin. Methods are given elsewhere (p. 463) for determining whether a substance is metabolically a glucose former. The crucial test usually employed is to administer the material in question to an animal whose liver has been depleted, as far as possible, of its glycogen by fasting, exercise, and exposure to cold. After a suitable period of time the animal is killed, or biopsies are made and the liver is examined for its glycogen content. In this way it can be shown that feeding the monosaccharides glucose, fructose, and galactose, and all other carbohydrates that give rise to these sugars, causes glycogen to be deposited in the liver.

As pointed out previously (p. 463), glycogen can be formed by the liver from a number of amino acids. To the extent that proteins furnish these amino acids, they must be regarded as potential glycogen-forming foods. Regardless of whether the immediate source of the amino acids is the diet (exogenous), the body tissues (endogenous), or the metabolic pool of amino acids, the processes are fundamentally the same.

Present evidence indicates that the higher fatty acids containing an even number of carbon atoms are not converted into glucose or glycogen in the animal body. On the other hand, propionic and other odd-carbon fatty acids are glycogenic. Those with 5, 7, 9, and 11 carbon atoms are split stepwise into fragments containing two carbon atoms and a final molecule of propionic acid; the former are ketogenic but not glycogenic, the latter is glycogenic but not ketogenic. Butyric acid is apparently the only even-carbon fatty acid which has definitely been demonstrated to be glycogenic. It is generally conceded that the glycerol of fat behaves in metabolism like sugar; there is no doubt that it is a potential glycogen former. Other glycogenic substances are lactic and pyruvic acids.

As indicated above, muscles contain an important store of glycogen. This is being used constantly in their metabolic activities and is restored primarily by synthesis from blood glucose. As the level of the latter falls, it is replaced in large part by glucose derived from liver glycogen by the process known as glycogenolysis. In this way the liver serves to maintain the normal percentages of blood glucose and muscle glycogen. However, not all of the muscle glycogen is synthesized from glucose originating from liver glycogen, since during absorption a portion of the glucose is transported directly into the systemic blood without first being synthesized into glycogen by the liver. From this glucose, muscle glycogen can be formed. Lactic and pyruvic acids in the muscles themselves or in the blood are also probable immediate precursors of muscle glycogen.

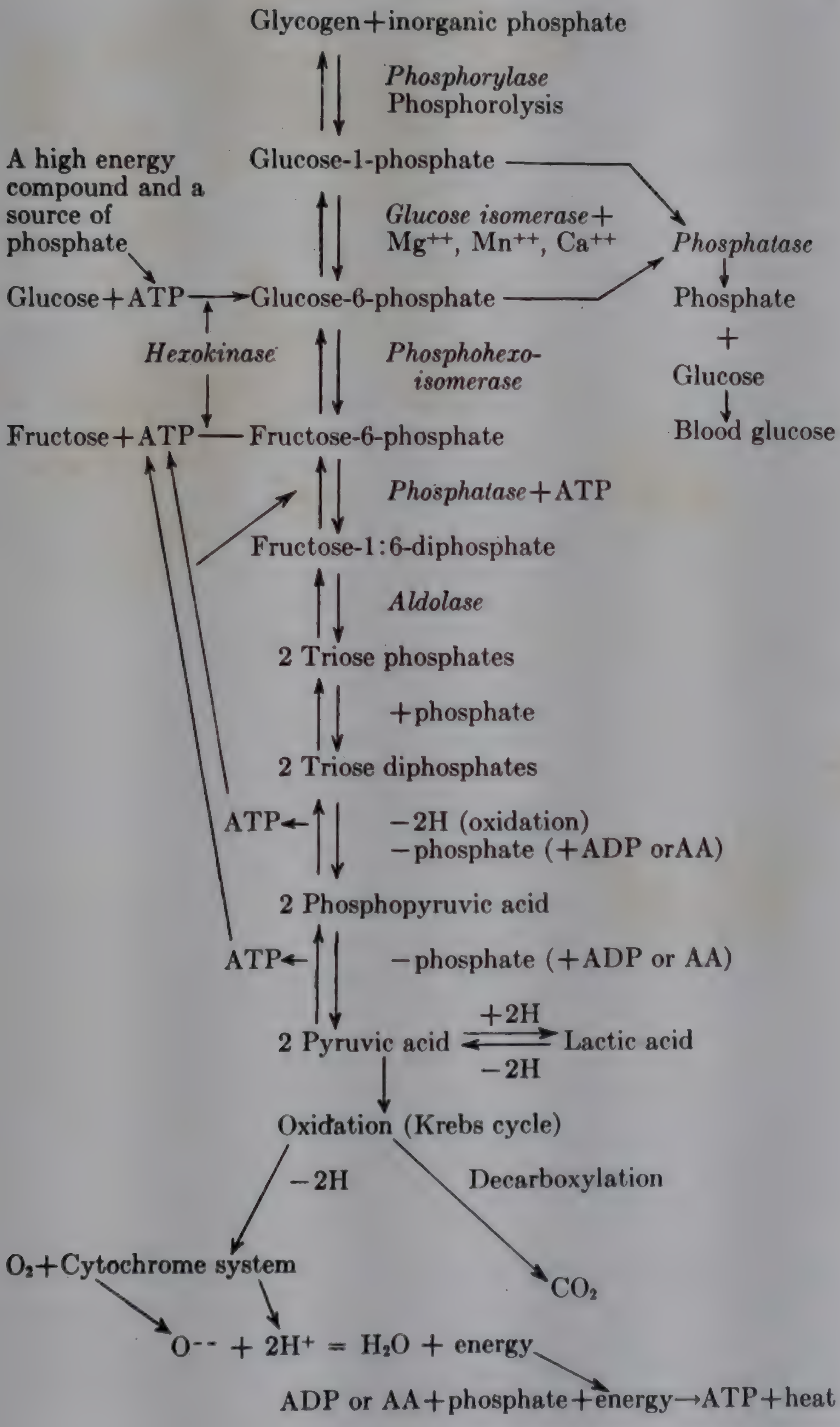
Formation of Glycogen. The monosaccharides, pyruvic acid, and lactic acid are direct glycogen formers. Other food materials are potential glycogen formers to the extent that they yield these substances in the animal body. The process of conversion of these into glycogen (glycogenesis) and the breakdown of glycogen into glucose (glycogenolysis) in the liver and into pyruvic and lactic acids in the muscles (glycolysis) is now known to involve a series of chemical reactions in which phosphate is essential; this breakdown process is spoken of as *phosphorolysis*. The principal steps involved in the synthesis and phosphorolysis of glycogen and the ultimate oxidation of its products to carbon dioxide and water are presented under the topic of physiological oxidations (p. 233). A knowledge of these processes is essential if one is to obtain an adequate understanding of the mechanisms of glucose storage as glycogen, its mobilization, and ultimate utilization in the animal body. It seems highly probable that before glucose and other monosaccharides can enter into the metabolic processes of the animal body, whether for storage or oxidation, they must enter this cycle. The point of entrance and the manner in which glucose enters this cycle, together with the general nature of the processes as they occur in liver, are as presented in the accompanying scheme.

The entrance of fructose into the cycle is similar to that of glucose except that it enters as fructose-6-phosphate. Since the processes listed are reversible, lactic acid, pyruvic acid, and other substances may enter the cycle at various points. The immediate fate of monosaccharides is the production of hexosemonophosphate.

The liver contains an enzyme *phosphatase* which removes phosphate from glucose-1-phosphate and glucose-6-phosphate to liberate glucose. This is the origin of blood glucose from liver glycogen.

It should be recognized, however, that the synthesis of glycogen from monosaccharides and other substances requires the expenditure of energy. This is supplied directly by the high-energy compound adenosine triphosphate (ATP), phosphate being transferred concurrently to glucose or fructose, and either adenosine diphosphate (ADP) or adenylic acid (AA, adenosine monophosphate) is formed. In order to have a ready supply of ATP for this purpose, it must be synthesized continuously; this also requires the expenditure of energy. Whenever energy is expended, heat is given off as a waste product since the chemical machinery has an efficiency of only about 25 per cent. The net energy liberated during glycolysis and the ultimate oxidation of pyruvic acid is stored in the synthesis of ATP and other high-energy phosphate compounds. Since ATP is used for the synthesis of both glucose-6-phosphate from glucose and fructose-1:6-phosphate from fructose-6-phosphate, synthesis of ATP must occur in later stages of the cycle. In the liver, only a small part of the glucose runs the fate of oxidation; most of it is poured into the systemic blood as blood glucose. That which is used for oxidative purposes serves to synthesize ATP, which embodies the net useful energy of these reactions that is available to the liver for synthetic and other metabolic processes. The remainder of the total energy expended is lost as heat. This may explain, in part at least, the specific dynamic action of carbohydrates.

The processes of carbohydrate storage and utilization are essentially similar in both liver and muscle with two important exceptions.


Glycogen + inorganic phosphate
Phosphorylase
Phosphorolysis
A high energy compound and a source of phosphate
Glucose-1-phosphate
Glucose isomerase +
Mg^{++}, Mn^{++}, Ca^{++}
Phosphatase
Glucose + ATP
Glucose-6-phosphate
Phosphate
+
Glucose
Blood glucose
Hexokinase
Phosphohexo-isomerase
Fructose + ATP
Fructose-6-phosphate
Phosphatase + ATP
Fructose-1:6-diphosphate
Aldolase
2 Triose phosphates
+phosphate
2 Triose diphosphates
ATP
−2H (oxidation)
−phosphate (+ADP or AA)
2 Phosphopyruvic acid
ATP
−phosphate (+ADP or AA)
+2H
2 Pyruvic acid
Lactic acid
−2H
Oxidation (Krebs cycle)
−2H
Decarboxylation
O_2 + Cytochrome system
CO_2
$O^{--} + 2H^+ = H_2O$ + energy
ADP or AA + phosphate + energy → ATP + heat

namely: (1) in muscles there is no phosphatase to liberate glucose from hexosemonophosphates, the cycle running to the pyruvic acid stage; and (2) ATP serves as the immediate source of energy for muscle contraction (p. 563). In glandular cells the process is similar to that in muscles.

OXIDATION OF GLUCOSE

Most of the energy produced by the normal animal comes from the oxidation of glucose; the final products of combustion are carbon dioxide and water. Before glycogen and other sugars can be utilized they must first be converted to glucose. Furthermore, before amino acids are oxidized for energy purposes they are first deaminated, after which certain ones are converted into glucose (Chapter XXIII). The evidence further indicates that before glucose can be oxidized it must be phosphorylated and pass through the metabolic steps indicated in the cycle just described. In the process glucose and fructose, after phosphorylation, are degraded stepwise through a series of phosphorylated compounds to pyruvic acid, which in turn, by some ten or more chemical reactions, is oxidized to carbon dioxide and water with the production of energy. The oxidation process is one of dehydrogenation; the hydrogen is transported by means of coenzymes to the cytochrome system, which removes an electron from it, thus forming H^+. The cytochrome system in turn is oxidized by transferring two electrons to oxygen, which if present serves as the hydrogen acceptor. The resultant $2H^+$ and O^{--} react to form water. The carbon dioxide which is produced in the oxidation of glucose and other substances is not formed, as was once believed, by the direct oxidation of carbon by molecular oxygen, but by decarboxylation (splitting-off of COOH) from intermediate organic acids in the Krebs cycle. The processes of oxidation by dehydrogenation and decarboxylation proceed in stepwise fashion until the metabolite is completely oxidized. A portion of the energy produced by these oxidative processes is utilized to resynthesize ATP from adenylic acid or adenosine diphosphate and a source of phosphate; the remainder is liberated as heat. More ATP is synthesized than is initially used in the phosphorylation process, and the potential energy of this net ATP represents the useful energy for muscle contraction, glandular secretion, absorption, and synthesis of various substances in the respective tissues.

Lactic acid is not a necessary intermediate in the process, but is produced only under conditions of relative oxygen want. In the absence of oxygen to receive the hydrogen removed in the oxidative processes, pyruvic acid accepts it and is reduced to lactic acid; this process is reversed when oxygen is made available. The final oxidative process of pyruvic acid, presumably according to the Krebs cycle, is fundamentally identical in both liver and muscle.

When lactic and pyruvic acids diffuse into the blood from the extrahepatic tissues, they are transported to the liver where they undergo conversion to glycogen or glucose. This indirect method is the only one by which muscle glycogen can become the source of blood glucose (Cori).

BLOOD SUGAR

The sugar present in the systemic blood under postabsorptive conditions is glucose; traces of other sugars may possibly exist. The amount of sugar present in the blood of different species is approximately as follows (see p. 54): cow, 40 to 60 mg. per 100 cc.; sheep, 40 to 65; goat, 43 to 65; pig, 40 to 250; horse, 60 to 110; dog, 70 to 100; chicken, 130 to 260; turkey, 175 to 210. Evidently the range of variation within and between the species is considerable. The low blood sugar level of ruminants, the high level of birds, and the great variability seen in pigs are worthy of note. In man the postabsorptive blood sugar level is 70 to 90 mg. per 100 cc. The blood sugar level of chickens is illustrated in Fig. 112.

Sugar may be added to the blood (1) by absorption from the alimentary canal, (2) by breaking down of the glycogen of the liver (glycogenolysis), and (3) by gluconeogenesis, or the formation of glucose from noncarbohydrate substances such as amino acids, glycerol, and possibly fat. Sugar may be removed from the blood (1) by oxidation, (2) by excretion through the kidneys, (3) by the formation of glycogen, and (4) by the formation of noncarbohydrate substances such as fat.

Most of the foregoing processes whereby sugar may be added to or taken from the blood have already been considered in some of their aspects in this or other chapters; a few of them, however, have not been treated. A subject which has not yet been discussed and which will involve a further consideration of several of these factors is the regulation of carbohydrate metabolism.

The Role of the Liver in the Control of the Blood Sugar Level. Modern work on the effects of removal of the liver in animals was begun by Mann and collaborators, who have studied this question extensively. Their principal findings have been verified and extended by numerous other investigators.

Removal of the liver is usually accomplished in several stages. An hour after the last operation, the animal (dog) is almost normal in appearance and remains so for several hours.

Then a period of severe illness quickly follows, which results in death in about two hours if the animal is untreated. The symptoms are "muscular weakness, loss of reflexes, flaccidity, return and exaggeration of reflexes, muscular twitching, and convulsions" (Mann, 1927). Blood analysis reveals a progressive fall in the blood sugar level, which is directly related to the development of the symptoms and death. The animal can be restored to an apparently normal condition by the administration of glucose. "The effect of the intravenous injection of glucose on an animal dying from removal of the liver is

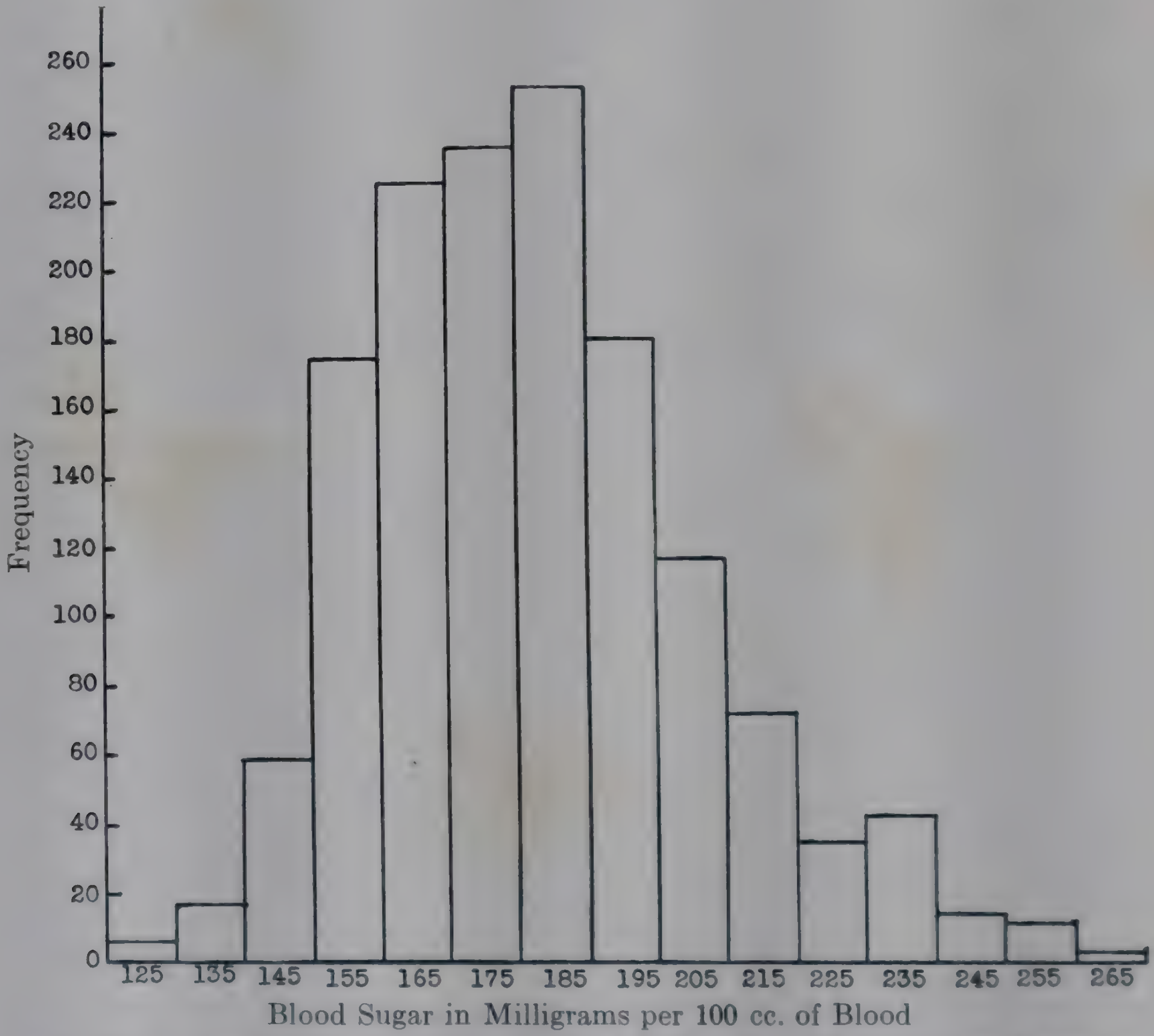


FIG. 112.—The fasting blood sugar level of the chicken (both sexes). (Batt, Thesis, University of Toronto, 1940a.)

one of the most remarkable of physiologic phenomena" (Mann, 1927). In less than a minute after they seemed to be dying, animals will walk, drink, and respond in an apparently normal manner. If convulsions are present at the time of the glucose injection, they disappear at once, consciousness returns, and in a short time the animals appear normal.

The liverless animal cannot be kept alive indefinitely by glucose injections. After a time secondary symptoms develop which result in death in spite of glucose administration.

To maintain the blood sugar of hepatectomized dogs at the postabsorptive level by the intravenous administration of glucose, it is necessary to infuse this sugar at a rate of about 250 mg. per kilogram of body weight per hour. In fasting animals this requirement is reduced to about 180 mg. per kilogram per hour. From these facts it has been concluded that the liver normally supplies an equivalent amount of glucose to the blood and that this supply is decreased during fasting. The liver provides this glucose from one or both of these sources: (1) breakdown of its glycogen to glucose (glycogenolysis), and (2) gluconeogenesis from proteins, fats, lactic acid, and other substances. Since the average quantity of liver glycogen is only about 1.5 gm. per kilogram of body weight, it is at most a 6- to 8-hour supply at the above rates of utilization. Taken alone liver glycogen is a relatively unimportant source of blood glucose during long periods of food deprivation. This is a practical point about which there has been considerable misunderstanding. Extrahepatic glycogen stores do not contribute appreciably to the maintenance of blood sugar, for muscle glycogen is only slightly decreased by fasting. It seems evident that the process of gluconeogenesis is quantitatively much more important than liver glycogen as a source of blood sugar in the absence of dietary sources.

The kidneys add glucose to the blood flowing through them, but the physiological importance of this source of sugar to the organism is not well understood.

Like fats, carbohydrates are energy-producing foods, but unlike fats they are *essential* energy producers. If carbohydrates are not supplied in the diet, glucose is produced by the liver either from dietary glycogenic substances or from mobilized body proteins or fats. During fasting or starvation, the dietary income of carbohydrates and other glucose formers being nil, the animal must depend upon its glycogen stores and upon endogenous gluconeogenesis for its glucose supply. Since fasting does not appear to affect significantly the ability of the extrahepatic tissues to utilize glucose (Soskin and Mirsky; Woodward), and since the available glycogen stores are limited, fasting animals soon reach a state of complete dependence on gluconeogenesis for a source of blood sugar. This occurs before the liver glycogen is depleted. It is now generally believed that gluconeogenesis takes place under practically all normal conditions, but varies in magnitude from time to time and is regulated physiologically. The rate of glucose production from proteins, whether from exogenous or endogenous sources, is indicated fairly quantitatively by the urinary nitrogen excreted. Gluconeogenesis plays the major role in maintaining a sugar supply to the blood and tissues during fasting and starvation. During the first postabsorptive hours of a fast (dog), the metabolism shifts from carbohydrates to proteins and fats. It must not be overlooked, however, that a large portion of these substances are converted, through gluconeogenesis, to glucose, in which form they are utilized by the tissues. The long-chain fatty acids, in part at least, are converted by the liver to ketone bodies and lower fatty acids and oxidized in these or similar forms.

The Effects of Fasting on the Blood Sugar Level. There are marked differences among the species in their ability to maintain normal blood sugar levels during fasting; the dog, cat, pig (Hanawalt and Sampson), and man seem to do it without difficulty. The reason for this appears to be a well-developed endogenous gluconeogenic mechanism. This involves two separate processes: (1) mobilization of body materials such as proteins and fats, and (2) the gluconeogenic activity of the liver. Evidence is accumulating to show that the control of

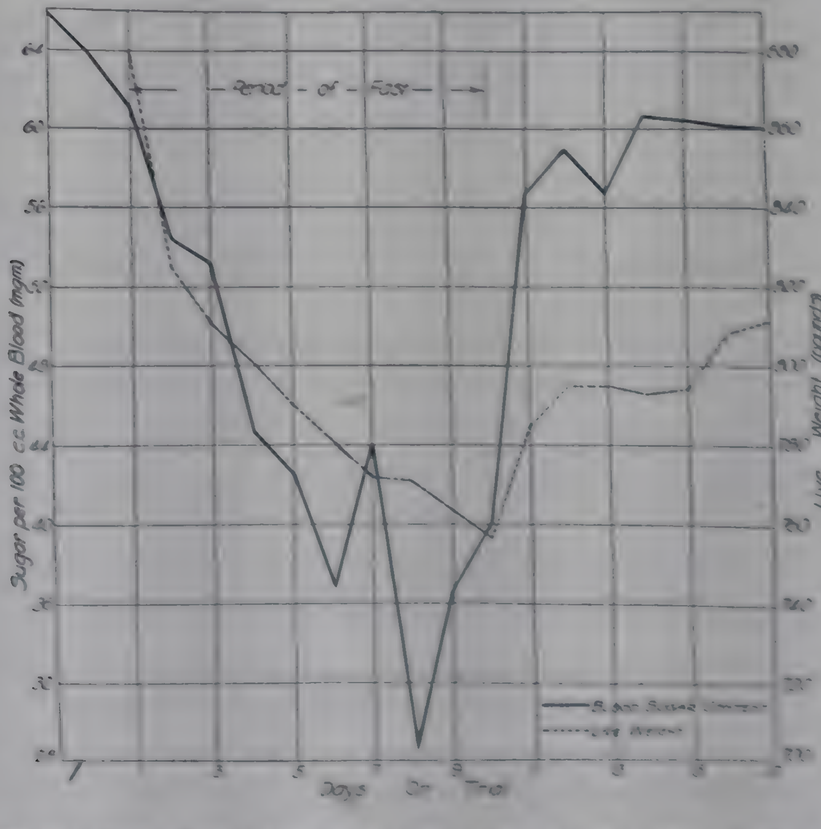


FIG. 113.—The blood sugar level and the weight of dairy cattle (five heifers) as influenced by fasting (9 days). The rise in blood sugar on the seventh day is accounted for by the fact that the cattle broke out of the paddock and ate some food the evening before. Note that the blood sugar level did not return to normal after feeding until several days had elapsed. (From Hodgson, Riddell, and Hughes. *Journal of Agricultural Research*, 1932, 44.)

mobilization is much the more important factor, gluconeogenesis in the liver being secondary to it. In cattle, fasting has been observed to cause a marked fall in blood sugar, which did not return to normal after feeding until several days had elapsed (Fig. 113). This is also true for the calf, but the return to normal is more rapid (Cook and Dye).

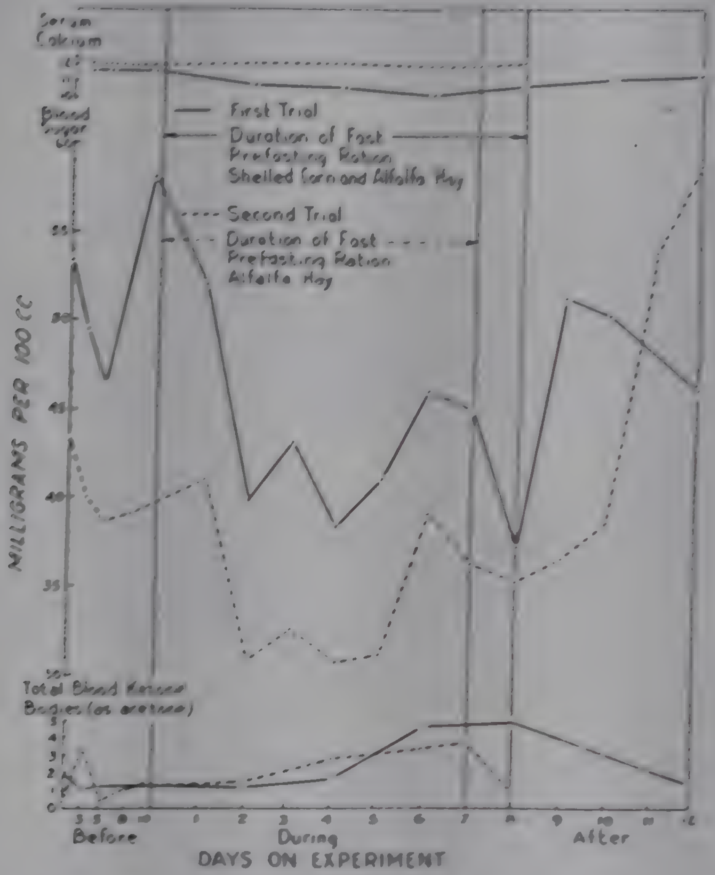


FIG. 114.—Effect of fasting on the levels of serum calcium, blood sugar, and blood ketone bodies in the ewe. The values are the averages for five animals. Two trials were run. The results of the first trial are shown by solid lines; the second by broken lines. (From Sampson and Boley, *Journal of the American Veterinary Medical Association*, 1940, 96.)

In the sheep the evidence is conflicting. Allcroft and Strand found that a fast of seven days did not alter appreciably the blood sugar level, whereas Sampson and Boley (1940) obtained a definite drop in their ewes during fasting (Fig. 114). In the diabetic calf the blood sugar will drop to hypoglycemic levels during fasting (Cook and Dye; McCandless). In depancreatized hens, rabbits, goats, pigs, and monkeys the blood sugar level usually drops to normal or below when the animals are fasted. In each of these species the gluconeogenic mechanism is presumably less well developed than in the dog, cat, pig, and man. The difference is probably in the mechanism for mobilizing body substances for gluconeogenesis since the liver is able to carry out this process from similar materials coming to it from the digestive tract.

Hypoglycemia in Newborn Pigs. Sampson and co-workers have described a disease of newborn pigs which is characterized by intense hypoglycemia and high mortality. Glucose therapy in the early stages of the disease may be effective, but in the terminal stages it is ineffective. A condition indistinguishable from the spontaneously occurring disease can be produced experimentally by fasting newborn pigs for 36 to 48 hours. The evidence indicates that hypoglycemia is the significant change in both conditions. Sampson and Graham have studied experimental insulin hypoglycemia in newborn pigs. In experimental insulin coma, "permanent functional damage of the brain and so-called irreversible coma as well as sudden death may ensue if pigs are maintained in a state of comatose hypoglycemia for approximately four or more hours. Injections of glucose hasten recovery from hypoglycemia of short duration, but may have little value in overcoming the effects of prolonged hypoglycemia." These three forms of hypoglycemia are illustrated in Fig. 115.

Weanling pigs, on the contrary, show only a moderate fall in the blood sugar level in fasting up to four weeks (Hanawalt and Sampson). In these animals the glucostatic mechanisms are evidently well established.

THE REGULATION OF CARBOHYDRATE METABOLISM

The metabolic history of glucose, particularly in relation to glycogen storage, blood sugar level, and carbohydrate oxidation, is markedly influenced by a number of regulatory mechanisms of which the following are most important: (1) glucose concentration in the blood, tissue fluid, and tissues; (2) insulin; (3) adrenaline, or sympathico-adrenal mechanism; (4) anterior pituitary hormones; (5) hormones of the adrenal cortex; and (6) the homeostatic function of the liver. The first two are concerned primarily with the rate of glucose storage and oxidation; the third, fourth, and fifth, primarily with mobilization of carbohydrate stores and of tissue substances for gluconeogenesis; and the last with regulation of the general blood sugar supply.

Glucose Concentration. A basic factor in the control of glucose utilization, either storage or oxidation, has been demonstrated experimentally to be glucose concentration (Wierzuchowski; Soskin and Levine; Bouckaert and de Duve). Up to a concentration which is sufficient to saturate the enzyme systems involved, glucose utilization is proportional to its concentration. This fact is explainable in terms of the law of mass action. The site of action of this concentration effect is apparently at the enzyme hexokinase, which catalyzes the phosphorylation of glucose, in the presence of ATP, to glucose-6-phosphate.

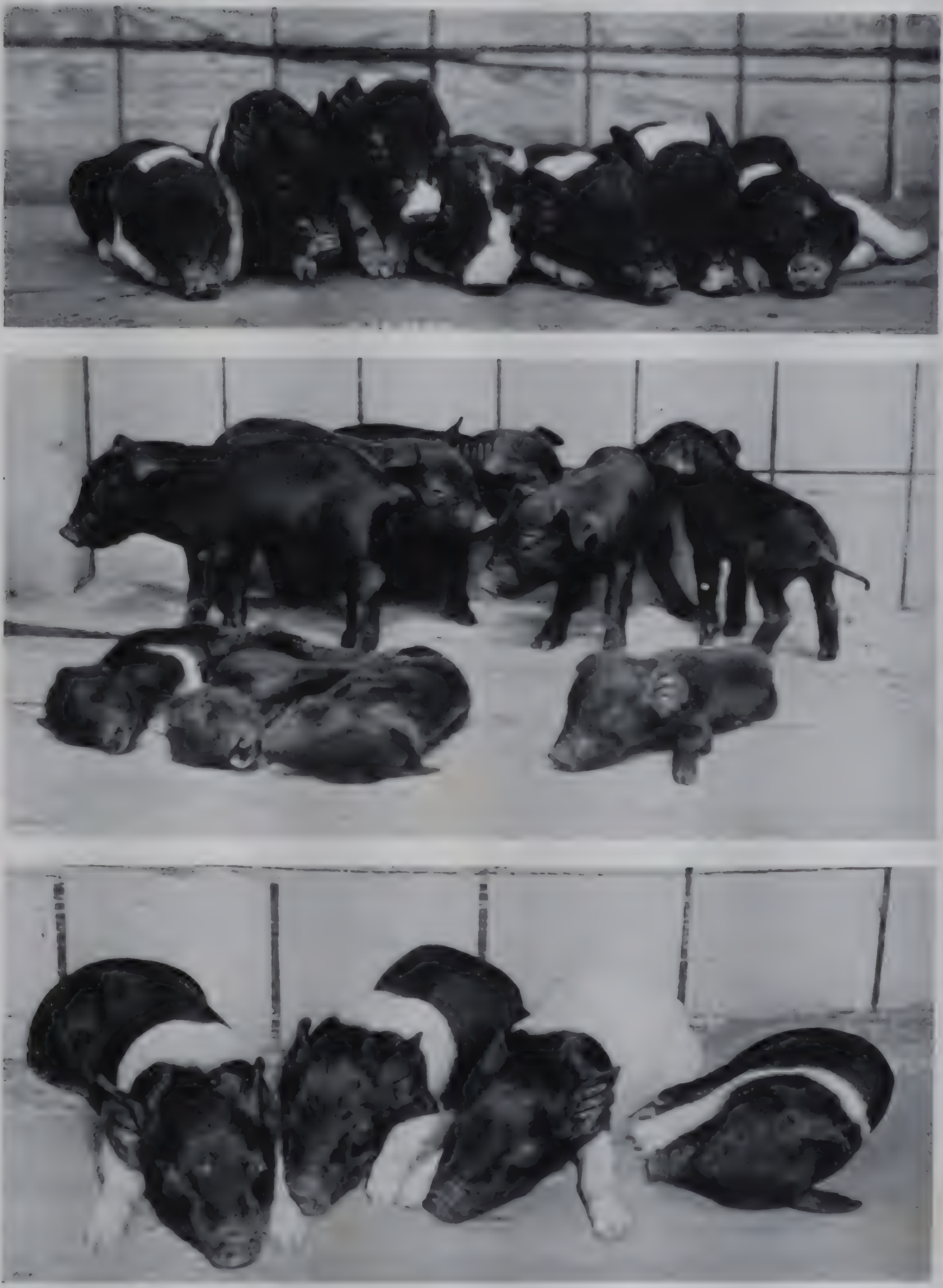


FIG. 115.—*Upper,* severe spontaneous hypoglycemia; *middle,* hypoglycemic coma produced by fasting; and *lower,* hypoglycemic coma produced by insulin injection, in newborn pigs. Increasing stupor and finally coma are manifested as the blood sugar level continues to fall below 40 mg. per 100 cc. Convulsions may or may not be observed in hypoglycemia of the pig. Note that in the middle figure the four control or nonfasted pigs show no symptoms of hypoglycemia. The normal range of the blood sugar level of newborn pigs is about 60 to 140 mg. per 100 cc., with an average of approximately 100 mg. (Courtesy of Drs. Sampson, Hanawalt, Hester, and Graham, College of Veterinary Medicine and Agricultural Experiment Station, University of Illinois.)

When the blood and tissue glucose is high, the rate of synthesis of this hexosephosphate is increased; both storage and oxidation of glucose are accelerated.

Insulin. It has been known for many years that removal of the pancreas causes an increase in the amount of sugar in the blood (hyperglycemia), the excretion of sugar in the urine (glycosuria), the development of a fatty liver, a rise of blood ketone bodies (ketonemia), and excretion of ketone bodies (ketonuria); in short, pancreatectomy causes diabetes. The antidiabetic function of the pancreas is dependent on the production of a hormone by the pancreatic islets. These are composed of groups of cells, different from those that secrete pancreatic juice, and scattered throughout the organ. Extracts of a pancreas whose cells of external secretion have been made to degenerate by ligation of the pancreatic duct, or extracts of fetal pancreas prepared prior to the development of the cells of external secretion, or alcoholic extracts of the pancreas of adult animals contain the hormone, which is designated as *insulin*. This hormone has been prepared in crystalline form and the evidence strongly indicates that it is a protein. Whether insulin owes its action to this large protein molecule or to a certain grouping of amino acids in the molecule is at present unknown (**Jensen and Evans**).

Being protein in nature, insulin is destroyed by proteolytic enzymes. This fact accounts for the early failures to obtain the hormone in extracts of the pancreas, and also accounts for its ineffectiveness when given by mouth.

Diabetes has more recently been produced by the administration of certain anterior pituitary extracts and also by the intravenous injection of alloxan, which lead to selective destruction of the β-cells of the pancreatic islets, the insulin-secreting cells. With these methods of producing diabetes the secretion of pancreatic juice and intestinal digestion remain undisturbed. Experimentally produced diabetes, regardless of the means employed, is not of the same severity in all animal species. In the dog and cat it is severe and usually terminates fatally. On the other hand, the hen (Batt, 1940a), duck (Sprague and Ivy), rabbit (Greeley), goat (Lukens, 1938), pig (Lukens, 1937), sheep (Jarrett; Dye and Woodward), and calf (Cook and Dye; McCandless and Dye) exhibit mild forms of diabetes. In general it seems evident that those animal species which are unable to maintain their blood sugar levels during fasting have mild forms of diabetes; those which do maintain approximately normal blood sugar levels during fasting develop severe diabetes by the methods described above.

The evidence strongly suggests that the hyperglycemia of diabetes is due largely to an increased rate of gluconeogenesis, but in part to a diminished storage of glucose in the liver and decreased oxidation of this sugar by the tissues. Both the hyperglycemia and ketonemia of diabetes depend upon the presence of a functional liver; hepatectomy or marked liver destruction by disease terminates both. In the diabetic animal all the metabolic process known to be affected by insulin can be promoted in the absence of this hormone provided the blood sugar concentration is sufficiently raised. *The diabetic animal at its characteristic high blood sugar level consumes as much sugar as the normal animal at its usual lower blood sugar level* (Soskin and Levine).

The Action of Insulin when Injected into the Diabetic Animal. Some of the features of pancreatic diabetes, whether the clinical form (man) or the experimental forms (dog, cat, and others), are as follows: The liver fails to form and retain glycogen and the rate of its formation in muscles is decreased, the ability of the tissues to oxidize glucose is diminished, the rate of gluconeogenesis is accelerated, the blood sugar rises, and glycosuria results. Accompanying the disturbances of carbohydrate metabolism, there is an increase in fat metabolism. This leads to an overproduction of the ketone substances in the liver; this increase may be so great as to produce a severe ketosis (p. 480). When insulin is given to a diabetic animal, the effect is to restore carbohydrate metabolism and these secondary disturbances to normal. The liver and muscles regain their ability to form and store glycogen, the tissues are again capable of oxidizing glucose in normal amounts, the respiratory quotient rises, and gluconeogenesis is reduced. These changes tend to restore the normal blood sugar level, and glycosuria disappears. In addition, fat metabolism is decreased and as a result ketone-body production and the existing ketosis disappear. When insulin is withdrawn, the manifestations of diabetes return.

The Action of Insulin when Injected into the Normal Organism. In the normal animal an optimal amount of insulin is being produced. Hence the injection of the hormone leads to an excess quantity in the body. Its effects under these conditions are qualitatively similar to those in the uninjected normal animal; the differences are quantitative only. Of all the actions of insulin that have been investigated, this hormone produces no metabolic changes other than those which can be produced by glucose itself (Bouckaert and de Duve). Injections of insulin into normal animals, in which hypoglycemia is prevented by the infusion of glucose, lead to an increase of glucose-6-phosphate and glycogen storage in both liver and muscle and an increase in the rate of glucose oxidation. The higher the insulin dose, the more it tends to act on the liver in contrast to the extrahepatic tissues; in other words, the more it tends to favor temporary storage of glucose as liver glycogen. At lower insulin levels, or if hypoglycemia develops as a result of excessive doses, its effects are greater on the extrahepatic tissues, particularly the muscles.

Severe insulin hypoglycemia, in fact severe hypoglycemia due to any cause, results in coma, and in some species convulsions, because of insufficient glucose for the metabolic requirements of the central nervous system. As a further result of the disturbed metabolism of the nerve centers, efferent impulses pass to the adrenal glands via the splanchnic nerves and cause an increased output of the hormone adrenaline. This stimulates the sympathetic nerves of the liver and accelerates the conversion of glycogen to glucose, which is added to the blood. However, this addition is insufficient to restore the blood sugar level to normal. Injection of glucose abolishes the symptoms of hypoglycemia.

The symptoms of hypoglycemia resulting from insulin dosage may be further considered. In general they are similar in all species but are by no means identical. A number of animals fail to show convulsions. This is true of the common fowl (Cassidy, Dworkin, and Finney), the sheep (Bodansky; Strand, Anderson, and Allcroft), the goat (Cutler), and the cow (Petersen, Hewitt, Boyd, and Brown). The pig behaves, in general, similarly to other animals (Magee and Harvey, Hanawalt and Sampson). Severe convulsions have been observed in the calf (McCandless and Dye).

Other symptoms are present. "In man, one observes hyperirritability, sweating, pallor, mental confusion, muscular weakness, tremors, a rise in blood pressure and basal metabolism and, finally, convulsive seizures. Some of these symptoms may be ascribed to the reflex discharge of epinephrine. After repeated convulsions, coma and death follow" (Cori). In the goat very large doses of insulin (at least 4 units per kilogram) are required to produce hypoglycemic shock, and the shock is evident only when the blood sugar has been kept at a low level (10 to 20 mg. per 100 cc.) for 5 to 8 hours. The symptoms of shock in the goat are apathy and sluggishness followed by coma. Convulsions are absent. Usually profuse salivation is present. Glucose injection gives prompt and complete relief. After-effects are apparently lacking (Cutler).

The stimulus for the secretion of insulin appears to be an increase in the blood sugar concentration. A nervous regulation of insulin secretion via the hypothalamus and vagi has been postulated on the basis of various experiments, but that this control is not very important is indicated by the fact that a transplanted pancreas is able to regulate blood sugar quite well.

The site of insulin action is probably the same as that of glucose concentration, namely, on the enzyme hexokinase, which catalyzes the phosphorylation of glucose, in the presence of ATP, into glucose-6-phosphate. Some believe that insulin activates or augments the action of the enzyme system involved in this process. The immediate fate of glucose with or without insulin is the same, namely, the synthesis of glucose-6-phosphate, the difference being quantitative and not qualitative. At any given blood glucose concentration, insulin leads to a relatively greater effect than would be produced by glucose alone, but by increasing the concentration of this sugar in the absence of insulin, the same quantitative change is possible. It may again be emphasized that of all the actions investigated, insulin produces no metabolic changes other than those which can be produced by glucose alone. The real action of insulin is to promote at low blood glucose concentrations effects which would occur without it only at considerably higher blood sugar levels.

Adrenaline. The hormone adrenaline or epinephrine has a profound effect on carbohydrate metabolism. When injected subcutaneously into animals it causes a distinct hyperglycemia as well as a marked increase in the lactic acid of the blood. Given intravenously its effect on carbohydrate metabolism is qualitatively similar but is quantitatively much less; the rise in blood pressure is, however, much greater. The reason why adrenaline given intravenously has less effect on carbohydrate metabolism is that it is quickly destroyed. When given subcutaneously it is absorbed more slowly and acts longer. Experiments have shown that the hyperglycemia seen after adrenaline injections is due to phosphorolysis of liver glycogen, whereas the increase in blood lactic acid is caused by the breakdown of muscle glycogen. Adrenaline is a mobilizer of liver and muscle glycogen; like insulin it increases the content of hexosephosphates in both liver and muscle. Its primary action, however, appears to be the acceleration of the phosphorolysis of glycogen and thus leads to an increased output of glucose by the liver and of pyruvic and lactic acids by the muscles. After a time, however, the liver glycogen begins to rise. This result is produced by one or both of the following: (1) the synthesis of liver glycogen from lactic or pyruvic acid which has escaped from the muscles into the blood and has been transported to the liver, and (2) increased storage of liver glycogen in consequence of an increased output of insulin by the pancreas as a result of the hyperglycemia.

Even though the liver is storing glycogen derived from lactic acid, glycogenolysis is still going on as is indicated by a continued rise of the blood sugar level. It is a case of glycogenesis exceeding glycogenolysis. In the hepatectomized animal adrenaline does not raise the blood sugar level, but it still causes a decrease in muscle glycogen and consequently an increase in the blood lactic acid. Not only does adrenaline affect the carbohydrate metabolism but it raises the metabolic rate. This calorigenic action is believed to be due to the oxidative energy required to reconvert lactic and pyruvic acids to glycogen.

Excitement, many drugs, ether and chloroform anesthesia, asphyxia, and other factors produce hyperglycemia in whole or in part via the adrenal mechanism.

Sheep from which the adrenals have been removed fail to show a rise in blood sugar and lactic acid when subjected to conditions (excitement, muscular exercise) that are known to increase them in normal sheep (Strand, Anderson, and Allcroft).

The Anterior Pituitary and the Adrenal Cortex in Carbohydrate Metabolism. The probable role of the anterior pituitary in carbohydrate metabolism has already been discussed in part in relation to diabetes (p. 496). Other pertinent experimental facts are the following: It has been shown that severe diabetes does not develop in the depancratized animal (dog, cat, and others) if the anterior pituitary is also removed. In such depancreatized-hypophysectomized animals (Houssay preparations), severe diabetes will develop when anterior pituitary extracts are injected. The same pituitary extracts will produce typical diabetic symptoms when injected into normal animals. When hypophysectomized animals are fasted, they develop severe hypoglycemia and its related symptoms. Experiments such as these have led several investigators to conclude that the anterior pituitary produces a diabetogenic hormone or factor. In a similar manner the ketosis of diabetes depends upon an anterior pituitary factor referred to by some as the ketogenic hormone. In all probability the primary role of these hormonal effects is to mobilize body proteins and fats to be processed by the liver for gluconeogenic and ketogenic purposes.

It is now generally recognized, however, that the role of the anterior pituitary as just indicated is, in large part at least, indirect via the adrenal cortex. The adrenotrophic hormone of the former stimulates the latter to produce its hormones and these in turn bring about an increase in endogenous gluconeogenesis. Whether the ketogenic action of the anterior pituitary is direct, indirect via the adrenal cortex, or both, is unsettled. Insulin inhibits the anterior-pituitary–adrenal-cortex mechanism and gluconeogenesis.

Lukens points out that the condition seen in the depancreatized goat and pig resembles that seen in the pancreatectomized-hypophysectomized carnivore. This fact also seems to be true for the calf, the sheep, and the chicken. It is possible that the anterior pituitary in these animals produces only a small amount of the diabetogenic factor, which, as indicated above, may be the same as the adrenotrophic hormone; or that some other endocrine difference exists.

The Homeostatic Function of the Liver. The liver plays a central role in blood sugar regulation and sugar tolerance. Its general functions in glycogenesis, glycogenolysis, and gluconeogenesis have been described. Independent of the hormone and nervous regulations just discussed, this organ has its own intrinsic action; its most important function in carbohydrate metabolism is the maintenance of a normal blood sugar level. This *homeostatic action* of the liver in regulating blood sugar has been studied quantitatively by Soskin and by Bouckaert and their co-workers. Although this is a primary function of the liver, it is markedly influenced by the blood sugar concentration, by insulin, and by the anterior-pituitary–adrenal-cortex mechanism. The balance between glucose storage, glucose mobilization, and glucose synthesis in the liver is influenced by each of these factors.

At the normal levels of insulin and anterior-pituitary–adrenal-cortex activity, there is a *hepatic threshold* (dog) of blood sugar (between 150 of 200 mg. per 100 cc of blood) at which glucose output from the liver is completely inhibited and at which sugar retention as glycogen occurs. Insulin lowers this hepatic threshold considerably, whereas an excess of the anterior pituitary diabetogenic factor apparently raises it. In diabetes the hepatic threshold is high; in fact the insulin supplied to the liver seems to play the primary role in determining this threshold.

Insulin not only increases glucose storage and oxidation at any given blood sugar level, but diminishes the utilization of both exogenous and endogenous proteins and fats for energy purposes. By these actions insulin effects a conservation of each of these substances by sparing or storing them for subsequent energy requirements or for other uses. The action of the anterior pituitary diabetogenic mechanism is one of mobilization and it opposes the conserving action of insulin.

Exogenous (Alimentary) Hyperglycemia and Glycosuria. When excessive amounts of glucose are introduced into the body, either by the alimentary canal or by subcutaneous or intravenous injection, the ability of the liver and muscles to store this sugar as glycogen may be so greatly taxed that an elevation of the blood sugar level and the appearance of sugar in the urine result. This condition, long designated as alimentary glycosuria, is better termed exogenous glycosuria (Macleod). The blood sugar level at which glycosuria occurs is known as the renal threshold for glucose. In man it lies at about 160 mg. of glucose per 100 cc. of blood; in the horse, at about 150 mg. (Link); in the chicken, between 260 and 310 mg. (Batt, 1940b); in the bovine, about 100 mg. (Bell and Jones).

The change in the blood sugar level (plotted as a curve) following the ingestion or intravenous injection of glucose is the basis of the *glucose tolerance test*. The term glucose tolerance is defined as the quantity of glucose which can be ingested, or preferably injected intravenously in most animals, without producing glycosuria. In ruminants the intravenous method is the only one which will give significant results. The injection of 0.5 to 1 gm. of glucose (50 per cent solution) per kilogram of body weight causes the blood sugar to rise abruptly to a maximum of about the kidney threshold for this sugar. The rate of decline is proportional to the glucose concentration and returns to the normal level in two or three hours in normal animals. A decreased tolerance for the sugar is indicated by a more marked hyperglycemia, a slower rate of fall, and return to normal only after four, five, or more hours. Usually the blood sugar curve drops slightly below the normal and later returns to the normal level.

Glucose tolerance depends primarily upon the homeostatic mechanism of the liver, but is influenced in a secondary manner by insulin and by the anterior-pituitary–adrenal-cortex mechanism. These exert their influence on the liver by altering the hepatic threshold, gluconeogenesis, and the rates of glucose storage and oxidation. At all times the exogenous income of glucose will summate with that being produced endogenously by gluconeogenesis. Under all conditions in which the latter process is proceeding at a high rate, a given injection, or other income, of glucose will cause a greater rise in blood sugar, an increased excretion of sugar by the kidneys, and a slower rate of decline to normal. If this is also accompanied by a decreased rate of glucose oxidation by the tissues, as in the diabetic animal, the condition will be aggravated. The glucose tolerance is decreased in diabetes and by fasting, starvation, low carbohydrate diets, or any condition in which the liver glycogen drops to a low level; it is increased by excess insulin and hypopituitary states. Fasting and starvation do not alter the rate of glucose oxidation by the tissues.

The glucose tolerance test is used extensively in clinical and physiological studies in man. The sugar is usually given orally, in amounts ranging from 50 to 100 gm., and the blood sugar curve followed for two or more hours. In normal persons the blood sugar level returns to normal in about two hours. In apparently normal pigs erratic blood sugar curves are often seen in glucose tolerance tests (Eveleth and Eveleth). In an average-size horse 50 gm. of glucose can be given intravenously in 10 minutes without reaching the renal threshold (Link). In mature cattle glucose feeding (1.75 gm. per kilogram in 50 per cent solution) causes little change in the blood sugar level, whereas in young calves the response is very marked (Kennedy and co-workers). The administration of either glucose or cane sugar by drench to ten adult bovines, in doses up to 8 gm. per kilogram of body weight, did not produce variations of blood sugar outside the range of normal fluctuations (Bell and Jones). Intravenous glucose tolerance tests in these same animals were associated with hyperglycemias which were proportional to the dosage of glucose injected. With the dose of 0.5 gm. per kilogram of body weight, the maximal blood sugar was 276 mg. per 100 cc., which returned to normal within 2 hours in all cases. The maximal glycosuria produced was 5.7 per cent; the maximal duration of glycosuria was 94 minutes. A possible explanation of the slight response in adult ruminants when the glucose is given orally is that it goes to the rumen where some of it is fermented to noncarbohydrate substances.

Chapter XXVI

MINERALS, WATER, AND VITAMINS IN METABOLISM

MINERAL METABOLISM

THE mineral, inorganic, or ash content of the body is represented by the material left after the body is incinerated. Tables in Chapter XXII show the composition of this ash with respect to a number of the elements. Present evidence indicates that the following mineral elements are required by the body for normal metabolic processes and must be present in the food: calcium, phosphorus, sodium, potassium, chlorine, magnesium, sulfur, iron, iodine, manganese, copper, zinc, and cobalt. The last five or six are often referred to as trace elements because they are required in such small amounts. Other minerals such as silicon, arsenic, bromine, aluminum, nickel, boron, etc., are found in the body in small amounts. No function in metabolism has been demonstrated for them. They may be present in the tissues incidental to their presence in the food. It is a question whether fluorine is an essential mineral.

The minerals yield no energy to the body, yet they play necessary roles in metabolism and nutrition. Calcium and phosphorus are required for the formation of bones and teeth. Other minerals, especially sodium, potassium, and chlorine, are concerned in the maintenance and regulation of the osmotic pressure, reaction, and other physicochemical properties of the liquids and juices of the body. Certain inorganic substances, notably potassium, calcium, and sodium, are necessary for the irritability and rhythmicity of heart and smooth muscle and the irritability of skeletal muscle and nerve. Others are in some way bound up in the living protoplasm as one of its integral parts or as essential elements in enzyme systems. They are probably just as important for the normal reactions of protoplasm as is protein, lipid, or water. Still others have special functions. These are considered in the following pages.

In the practical nutrition of farm animals, apparently the only minerals that are ever deficient are sodium and chlorine (fed as common salt), phosphorus, calcium, iodine, iron, copper, cobalt, and manganese. Except in a few special areas, iron deficiency in the food is a practical problem only during the suckling stage in pigs. Cobalt and copper deficiencies in the soil and food occur only in certain areas of the world. Manganese deficiency is a practical problem only in poultry nutrition. Sodium and chlorine are the only inorganic substances that are regularly deficient in the foods of farm animals.

The occurrence in this country of mineral nutritional diseases in animals is shown on the accompanying map (Fig. 116) and is discussed in a recent article by Beeson. It is beyond the scope of this book to give an extensive discussion of the mineral nutrition of farm animals in health and disease. For further information on this topic, the following references will be found useful: Maynard, 1941, 1947; Maynard and Loosli; Huffman and Duncan; Bohstedt; Udall; and the several reports on the nutritive allowances for animals by the Committee on Animal Nutrition of the National Research Council (dairy cattle, Loosli and associates; beef cattle, Guilbert and associates; sheep, Pearson and associates; swine, Hughes and associates; poultry, Cravens and associates). For minerals in the nutrition of the dog, see the book by McCay.

Calcium and Phosphorus. These substances are so closely related in metabolism and nutrition that they may well be discussed together. They constitute much the greater part of the mineral matter of the body, and are found in greatest amounts in bones, where they occur as $Ca_3(PO_4)_2$ and $CaCO_3$. These salts do not exist in the free state but are in some way combined with each other. Roentgen-ray and other physical studies on the structure of bone indicate that the latter belongs to the apatite series.

The concentration of calcium in blood serum varies in different mammals from 9 to 15 mg. per 100 cc. (p. 54). The serum calcium is made up of diffusible and nondiffusible portions. The former is ionized; the latter is protein-bound.

In the laying hen a high serum calcium concentration is present (15 to 40 mg. per 100 cc.). The cause of the rise in the serum calcium level accompanying laying is not well understood. The work of Altmann and Hutt suggested that a hormone produced by the ovary stimulates the parathyroids, but this theory is not supported by the more recent studies of Marlow and Richert. Conrad has shown a relationship between high environmental temperature and the calcium level in the blood of the laying hen. An increase in temperature caused a decrease in the calcium level. Riddle has studied the cyclic changes in calcium, phosphorus, and fat of the blood as related to egg laying and the production of estrogen.

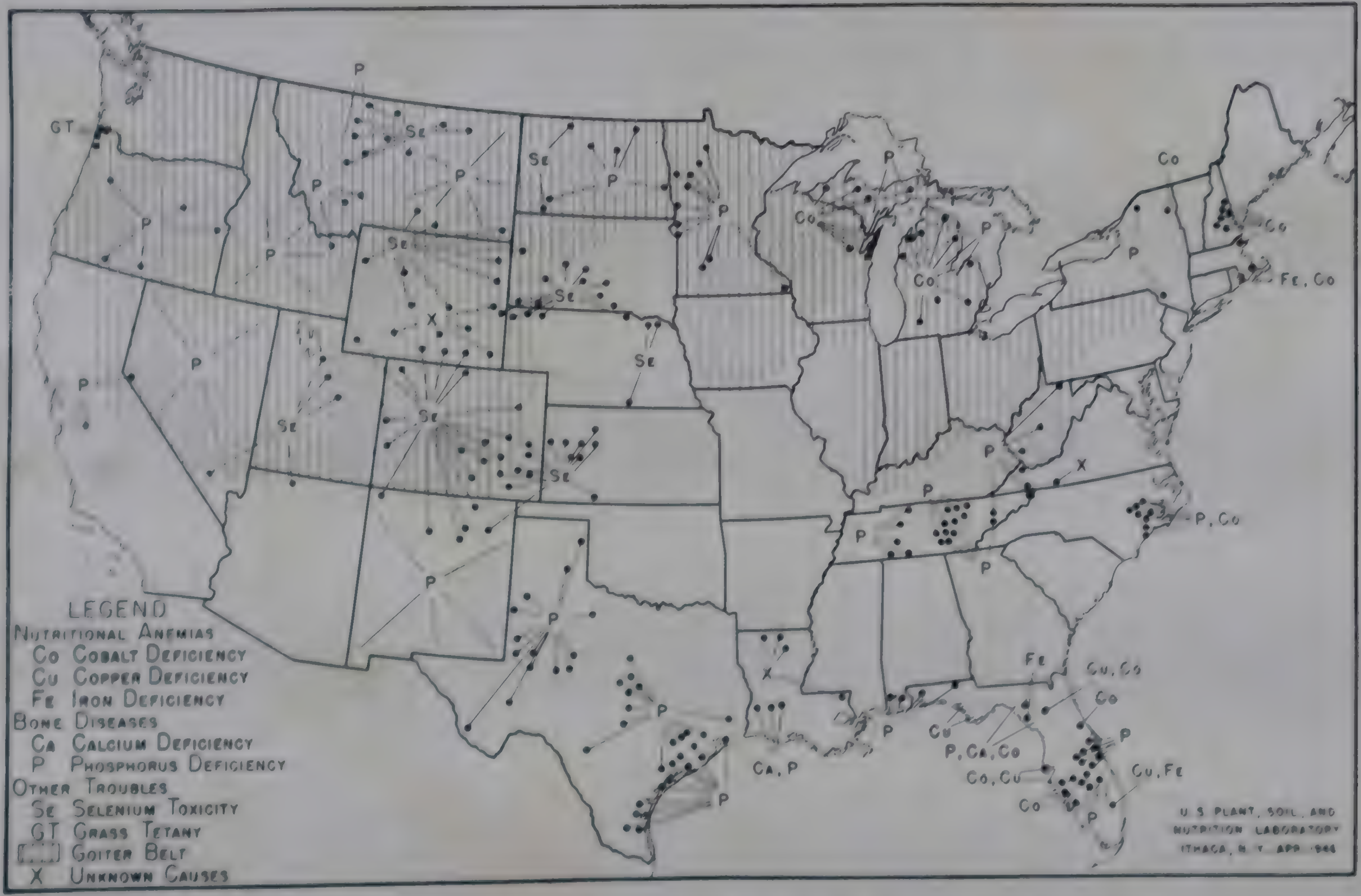

LEGEND
Nutritional Anemias
Co Cobalt Deficiency
Cu Copper Deficiency
Fe Iron Deficiency
Bone Diseases
Ca Calcium Deficiency
P Phosphorus Deficiency
Other Troubles
Se Selenium Toxicity
GT Grass Tetany
Goiter Belt
X Unknown Causes
GT
Fe, Co
P, Co
Cu, Co
P, Ca, Co
Co, Cu
Cu, Fe
Ca, P
U. S. PLANT, SOIL, AND
NUTRITION LABORATORY
ITHACA, N. Y. APR. 1944

Fig. 116.—Occurrence of mineral nutritional diseases in animals. The dots show the approximate location of the observed deficiency. The lines not terminating in dots indicate a generalized area where specific locations have not been reported. The goiter region is also a generalized area.

The concentration of inorganic phosphorus in blood serum ranges from 2 to 11 mg. per 100 cc. in different animals (p. 54). It is believed that inorganic phosphorus is practically absent from the cells of the circulating blood. However phosphorus in organic combination is present in large amount in the cells. In general it may be said that the concentrations of Ca^{++} and PO_4^{---} in the circulating plasma stand in reciprocal relation to each other. An increase in the concentration of one results in a decrease in the concentration of the other.

Growing, pregnant, and lactating animals require liberal amounts of calcium and phosphorus in their diets. For proper nutrition it is necessary that these elements be present in the food in adequate amounts, and in some species it is necessary or desirable that they be present in a certain ratio to each other. When the intake of either is too high or too low, the absorption of the other from the intestine is interfered with. In practical nutrition a ratio of calcium to phosphorus in the food of 1:1 to 2:1 is usually recommended.

The metabolism of calcium and phosphorus and that of vitamin D are closely interrelated (p. 522). When these interrelations are not normal, rickets tends to develop owing to failure to deposit proper amounts of tricalcium phosphate in the bones. When the supply of vitamin D is adequate, less favorable Ca:P ratios do not cause trouble. When the ratio is unfavorable and vitamin D is present in inadequate amounts, deficient bone calcification and rickets will result even though the calcium and phosphorus supplies are very liberal. Apparently in cattle a rigid Ca:P ratio in the diet is not required (Bohstedt). Possible reasons are a species difference in the metabolism of calcium and phosphorus and the consumption of large amounts of sun-cured hay. The parathyroid hormone (p. 700) is also a regulator of calcium and phosphorus metabolism.

The availability of the different calcium salts (lactate, carbonate, phosphate, silicate, sulfate) does not appear to vary greatly. Cereals, tubers, roots, and the grass hays are calcium-poor, whereas milk, leaves, and legumes are calcium-rich. Milk, the grains, and meat are good sources of phosphorus. The roughages are phosphorus-poor.

When the draft on body calcium is large, an animal may show a negative calcium balance in spite of an adequate amount of calcium in the diet. This means that the amount represented by the negative balance must have come from the calcium stores, principally the bones. This condition is seen particularly in high-producing dairy cows during the first half of the lactation period when fed winter diets (Forbes, 1927). The calcium balance remains negative in spite of the addition of large amounts of calcium to the diet—for example, precipitated bone, calcium carbonate, calcium chloride, calcium lactate. However under very favorable conditions of feeding, positive calcium balances in high-producing dairy cows have been noted. Substantially the same statements apply to phosphorus. The mineral metabolism of beef steers is not characterized by the negative balances seen in milk-producing cows (Forbes, French, and Letonoff). The paths of calcium excretion are the kidney and the intestine.

The principal known functions of calcium are as follows: (1) It is of paramount importance in the formation of bone and teeth. Its importance in skeletal growth is well shown in Fig. 117. (2) It is present in all cells and is in some obscure way necessary for their functioning. (3) Because calcium is excreted chiefly by the bowel it has special significance in the regulation of reaction in the organism. (4) It is concerned in the coagulation of blood and milk. (5) It is related to the irritability of muscle and nerve.

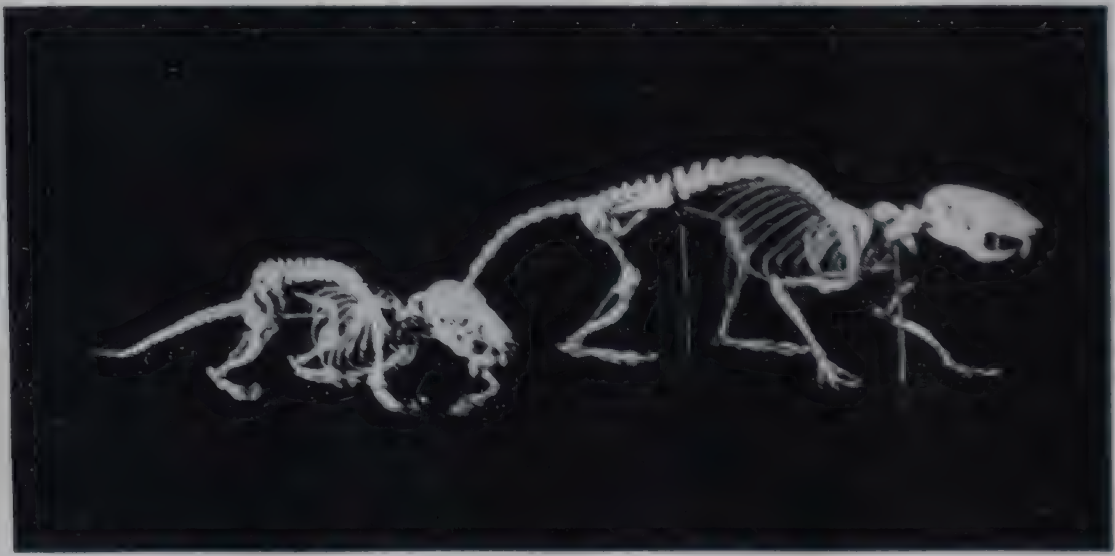


FIG. 117.—Showing the importance of calcium in skeletal growth. The skeletons are of twin-brother albino rats. One rat received a diet containing a normal amount of calcium (wheat, meat, and milk), whereas the other rat received a diet containing a low amount of calcium (wheat and meat). (From Sherman and MacLeod, *Journal of Biological Chemistry*, 1925, 64.)

The known functions of phosphates may be summarized as follows: (1) They are concerned in the maintenance of a proper reaction in the blood. (2) With calcium, they are of great importance in the formation of bone and teeth. (3) They are necessary in the maintenance of a normal calcium concentration in the blood. (4) They play a necessary part in carbohydrate metabolism and the transfer of energy in muscle contraction.

Phosphorus deficiency in the soil occurs in many parts of this country and of the world. This leads to a deficiency of the element in plant products of the soil and may cause serious disorders and economic losses in herbivores. In phosphorus deficiency in cattle there is a decrease in the inorganic phosphorus of the blood, poor appetite, and a gradual failure of milk production. Depraved appetite, or pica, may be evident later. Range animals may chew bones or eat parts of carcasses. Bone malformations known as low-phosphorus rickets in young cattle and as osteomalacia or osteoporosis in older animals are seen in chronic phosphorus deficiency.

Similar deficiency of calcium may occur but it is much less widespread, and the symptoms are mild. In prolonged deficiency, depletion of the calcium and phosphorus of the bones may cause increased bone fragility and fractures.

Schmidt (1940) has discussed calcium and phosphorus deficiencies in cattle and horses.

Parturient Paresis. This condition, known also as milk fever, occurs in dairy cows shortly after calving. When fully developed there is paralysis and unconsciousness, but in the earlier stages there may be muscular spasms and other symptoms of increased irritability of the central nervous system. In parturient paresis there is a definite lowering of the serum calcium level; the fall may be as much as 70 per cent. The hypocalcemia is usually regarded as having causal relation to the disease, but the factors operating to produce the fall in the level of the serum calcium are doubtless complex and they are poorly understood. The acute hypocalcemia is believed to be brought about, at least in part, by the heavy demands imposed on the blood calcium by the sudden onset of profuse lactation. It has been postulated that parathyroid insufficiency is the basic cause of the failure to mobilize adequate amounts of calcium. The treatment of milk fever consists of inflation of the udder with air or the injection of a calcium salt (usually calcium gluconate) intravenously. The udder inflation is believed to be effective because of stopping the secretion of milk by exceeding the secretory pressure of the mammary gland. Thus the drain on the blood calcium is stopped.

That hypocalcemia is the fundamental physiological change in milk fever has recently been questioned by Craige and Stoll. They suggest that hypocalcemia, although a characteristic sign of the disease, may be secondary to a more fundamental alkalosis in this condition. Evidence in favor of this view has been adduced, but the validity of the hypothesis must be tested by further work.

Magnesium. Although it has long been believed that magnesium is essential to life, proof of its indispensability has been obtained only in recent years. Kruse, Orent, and McCollum fed rats a diet containing only 1.8 parts per million of magnesium but adequate in other respects. Rats restricted to this diet become ill and soon die. The principal symptoms are vasodilatation, increased nervous irritability, cardiac arrhythmia, and convulsions. Similar symptoms occur in dogs. The tetany seen in hypomagnesemia is designated as magnesium tetany.

The concentration of magnesium in the blood plasma ranges from approximately 2 to 4 mg. per 100 cc. The corpuscles contain 2 to 12 mg. per 100 cc. of corpuscles. Eveleth has studied the distribution of magnesium in the blood cells and plasma of animals of many species. Duncan, Lightfoot, and Huffman emphasize the normal variability of the plasma magnesium level in dairy calves and draw attention to a seasonal change in the concentration, a considerable drop occurring during the transition from winter to summer conditions. In mature beef cattle at pasture Allcroft and Green have noted lower values in winter than in summer. Levels as low as 0.5 mg. per 100 cc. without symptoms of nervous hyperexcitability or of tetany were observed. The grass contained an adequate amount of magnesium.

Magnesium tetany, sometimes resulting in death, has been produced in calves by feeding a diet of milk or milk with supplements. The tetany was accompanied by low blood magnesium levels but normal calcium and inorganic phosphorus (Duncan, Huffman, and Robinson).

Calves fed diets sufficiently lacking in magnesium to cause the blood magnesium to be reduced to a low level showed definite lesions at autopsy. Depositions of calcium salts occurred in the yellow elastic fibers of the endocardium, great vessels, spleen, and other organs. The Purkinje fibers were degenerated and calcified. Hepatitis and nephritis were noted (Moore, Hallman, and Sholl). Tetany associated with hypomagnesemia has been reported to occur clinically in cattle by several investigators (Metzger), and a disease of cattle associated with hypomagnesemia and hypocalcemia has recently been reported from Oregon. There was no deficiency of magnesium or calcium in the diets (Muth and Haag).

Magnesium sulfate administered continuously by intravenous injection in adequate amounts causes changes in the heart rate and intracardiac conduction as revealed by electrocardiographic studies. At first there is tachycardia, followed by bradycardia. All phases of intracardiac conduction are depressed (Smith, Winkler, and Hoff).

Given in large amounts parenterally, magnesium is a depressant to the central nervous system and has a peripheral curarelike effect (Goodman and Gilman).

Iron, Copper, and Cobalt. In the animal body *iron* is best known as a component of hemoglobin and its importance in this connection cannot be overestimated. However, iron occurs in other situations in the body. All tissues contain iron but the chemical nature of the iron compounds in the tissues is not well understood. Some of this iron is in nonhematin form, whereas part of it is in hematin compounds. Ferrous iron in inorganic form may occur in the tissues. Although most of the iron of the blood occurs in hemoglobin, at least two other iron fractions in blood have been identified in recent years. One of these occurs in the plasma, the other in the red corpuscles. A significant amount of the iron of the body occurs in myoglobin. The storage depots for iron are mainly the liver, spleen, and bone marrow.

The question has frequently arisen whether or not the body can utilize inorganic preparations of iron for hemoglobin formation. It is now generally agreed that inorganic iron can serve as the source of iron for the formation of hemoglobin. In fact, it is actually superior to some organic forms.

Radioactive iron, "marked" iron, has recently been used in studies of iron absorption, transport, and utilization (Hahn and co-workers, 1939). The radioactive iron was fed to dogs, both anemic and normal, following which procedure measurements of radioactivity of viscera and blood were made. It was found that iron absorption is determined, in some unknown way, by the need of the body for iron. In normal dogs not requiring iron there is only slight absorption. In anemic dogs prompt assimilation of the iron occurs. The plasma was shown to be the medium of iron transport from the digestive tract to the place where it is utilized. Significant amounts of radioactive iron were found in the red cells in a few hours after its administration. That the liver and bone marrow are important in iron metabolism was confirmed by this work. Hahn and co-workers (1943) have confirmed and extended these studies. Under normal conditions there is very little absorption of iron from the gastro-intestinal tract, for normally very little iron is lost from the body. Small amounts are excreted in the bile. However, when anemia is induced, as by bleeding, absorption of iron from the gastro-intestinal tract becomes active in about 7 days. Little absorption occurs normally because the gastro-intestinal mucosa is saturated with iron. A "mucosa block" for iron exists. Desaturation requires days, as after hemorrhage. Then active absorption can occur. Iron is absorbed from the stomach as well as the intestine.

Milk contains very little iron, cow's milk only about 0.5 mg. per liter. Animals are born with a considerable store of iron in their bodies, especially in the liver. In most species this is sufficient to prevent nutritional anemia until the young animal begins to eat other foods. Under conditions of confinement, however, when there is no access to soil or forage, suckling pigs frequently develop nutritional anemia with very low hemoglobin levels. This condition can be prevented, or cured in the early stages, by the administration of iron and a trace of copper (Fig. 118). Untreated, the disease is highly fatal.

Modern work demonstrates that *copper* is essential for iron utilization in hemoglobin formation (Elvehjem, Schultze). Copper is not a part of the hemoglobin molecule nor does it appear to be an essential part of the framework of the erythrocytes in the circulation. Copper probably acts as a catalyst in hemoglobin formation, and it may be of importance in enzyme actions in the body. Copper occurs in small amounts in the blood, the concentration being about 0.2 mg. per 100 cc. Its distribution between plasma and corpuscles is about equal. It is present in all living matter.

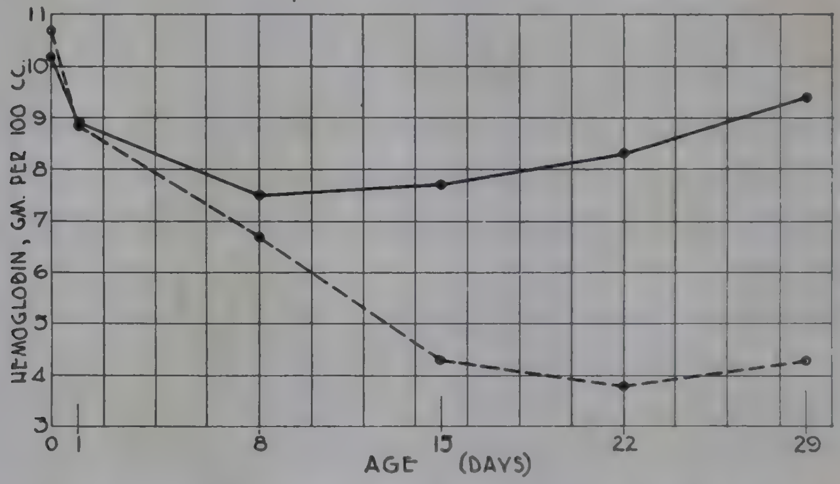


FIG. 118.—Showing the effect of iron and copper (iron citrate and copper sulfate) administration on the hemoglobin content of the blood of suckling pigs. The solid line indicates the average hemoglobin content of the pigs that received iron and copper. The broken line indicates the average hemoglobin content of littermate controls, not receiving iron and copper. (Data of Hamilton, Hunt, Mitchell, and Carroll.)

Copper-deficient areas occur in several parts of the world, and animals, particularly ruminants, grazing in these areas show disorders associated with copper deficiency. Copper deficiency has been reported in Florida.

Recent evidence shows that another mineral is essential for the prevention of progressive emaciation and anemia, at least in some species of animals. It is *cobalt*. There occurs in Florida a nutritional anemia of cattle known as salt sick. Where cobalt is lacking in the forage, iron and copper are ineffective in curing the condition. Cobalt is also required (Neal and Ahmann). Evidence has recently been obtained of a cobalt deficiency in cattle in parts of Michigan (Killham), Wisconsin (Geyer and co-workers), New Hampshire, North Carolina, and New York (Fig. 116, p. 506). Diseases of ruminants in Australia, New Zealand, and other parts of the world due to cobalt deficiency have been reported (Marston). Cobalt exerts a favorable effect on hematopoiesis in some dogs on a milk diet with iron and copper. Other dogs on the same diet may show no stimulation of hematopoiesis when cobalt is administered (Frost, Elvehjem, and Hart).

Cobalt excretion from the body has been studied by the use of radioactive cobalt (Greenberg and co-workers). When cobalt is introduced parenterally into the body, the chief path of its excretion is the urine. Much smaller amount are eliminated in the feces. When given by mouth much of the cobalt is unabsorbed, as is indicated by the appearance of a large proportion of the element in the feces.

Sodium, Potassium, and Chlorine. Sodium salts occur mainly in the fluids of the body, whereas potassium salts are more abundant in the cells. Of the sodium salts, the chloride is present in greatest amounts. This salt is peculiar in that man deliberately adds large amounts of it to his own diet and in that it is craved by many animals, especially herbivores. Years ago, Bunge, on the basis of some experiments on himself, propounded the theory that sodium chloride craving is due to the presence of excessive amounts of potassium salts in the diet of vegetable feeders. These salts upon entering the body were supposed to cause the excretion of excessive amounts of sodium and chloride, thus leading to sodium chloride hunger. That Bunge's theory does not hold, at least for growing pigs, is indicated by the work of Richards, Gordon, and Husband, who found that an excessive potassium content of the diet has little effect on the excretion of sodium or chloride. In this same connection Theiler, Green, and Du Toit have shown that a relatively high ratio of K to Na in cattle is not productive of specific disease. It seems certain that the craving of vegetable feeders for salt is due more to a deficiency of sodium and chlorine in foods of plant origin than to any specific K:Na antagonism.

The rates of absorption of sodium, potassium, chlorine, and other minerals have been studied in man by the use of radioactive isotopes (Hamilton). The radio-sodium was given in the form of NaCl, the radio-potassium in the form of KCl, and the radio-chlorine in the form of LiCl. The radioactivity of the hand, as measured by a Geiger-Müller counter, was used to indicate absorption. The rates of absorption of sodium and chlorine were rapid, radioactivity of the hand manifesting itself within 3 to 6 minutes after ingestion. Absorption appeared to be complete within 3 hours. The absorption of potassium was slower. It took 6 to 15 minutes for radio-potassium to appear in the hand after ingestion. The period of absorption lasted 5 hours.

The effects on animals of diets very slow in sodium have not been extensively studied. Orent-Keiles and co-workers restricted rats to a diet containing only 0.002 per cent of sodium but adequate in other respects. A train of symptoms developed which resulted in death. Retarded growth, eye lesions, and disturbances of the reproductive functions were the principal manifestations.

The same investigators studied the effects of chlorine deprivation. Growth was retarded but no other symptoms developed during a period of 90 days. A diet low in both sodium and chlorine also led to retarded growth, as well as severe alopecia. The growth retardation in neither case was so great as that seen with a sodium-low diet.

The fowl has been found to be very sensitive to small amounts of sodium chloride in the drinking water. Solutions of the strength of physiological saline proved to be very toxic for chicks. The resulting pathological state was characterized by nephrosclerosis and disturbances of water metabolism. Mammals take 1 to 2 per cent sodium chloride solutions instead of drinking water with no apparent ill effect (Selye).

The effect of potassium deprivation in rats has been studied in McCollum's laboratory. Growth was slow but steady. Sexual maturity was retarded. Pregnancy failed to occur. The animals were restless, and depraved appetite was evident. Cardiac slowing and arrhythmia were present, and myocardial damage was found at autopsy.

The potassium requirements of growing pigs has been studied by Hughes and Ittner. In pigs receiving no potassium in the diet, the first indication of the deficiency was reduced appetite. Unsteadiness, inability to rise, loss of weight, emaciation, and death followed. At autopsy the mucous membrane of the gastro-intestinal tract showed pathological changes.

Calves on a diet low in potassium show a distinct prolongation of the QRS interval of the electrocardiogram (Sykes and Alfredson) and degenerative changes in the Purkinje fibers of the heart (Sykes and Moore).

Under practical conditions of animal nutrition a potassium deficiency is probably never present.

Iodine. See p. 693.

Sulfur. See p. 422.

Manganese. This substance is believed to be a normal constituent of practically all tissues. The manganese content of the blood in different species has been reported to range from 0 to 0.02 mg. per liter of blood. It is stored mainly in the liver and kidney, and is eliminated by the colon, in the bile, and in the urine. Although the normal functions of manganese are poorly understood, the evidence indicates that it is necessary for proper bone formation, growth, and reproduction. It has been suggested that manganese is concerned in tissue respiration, possibly acting as a coenzyme and to accelerate phosphatase activity in bones. *Perosis* is a malformation of the bones of chicks and poults. It is apparently a complicated deficiency disease, a lack of manganese being one of the factors responsible for its production. Choline and biotin, members of the vitamin B-complex, are also concerned in the production of perosis. Manganese deficiency has been produced experimentally in rabbits. Bone development is seriously affected, both grossly and microscopically. Testicular degeneration occurs (Smith and co-workers). Rats on manganese-deficient diets show impaired growth, slight anemia, defective bone formation, and a high blood serum phosphatase (Wachtel, Elvehjem, and Hart). Swine kept for months on rations very low in manganese show slight or doubtful evidence of manganese deficiency (Johnson). This does not mean that swine do not need manganese, but it does demonstrate the improbability of the occurrence of manganese deficiency in swine when fed normal diets under natural conditions.

In practical nutrition manganese deficiency is not a problem except in poultry under some conditions.

Zinc. Modern work shows that zinc is a dietary essential. Rats on diets very low in zinc do not grow as well, either as to rate or maximum weight attained, as control rats on rations containing zinc. The functions of zinc in the body are not well understood. It occurs in the enzymes carbonic anhydrase and uricase and is a part of crystalline insulin. It is widely distributed in the body and appears to be associated with proteins. The elimination of radioactive zinc has been studied (Montgomery and co-workers). Introduced intravenously as zinc chloride, labeled zinc appears in pancreatic juice, duodenal juice, and bile, as determined on animals with appropriate fistulas for collecting the juices. The amount eliminated in the bile was very small, but the other juices contained large amounts. Only a small amount of radioactive zinc is excreted in the urine (Sheline and co-workers).

Zinc deficiency in the food under practical conditions apparently never occurs.

Fluorine. This element is widely distributed, in very small amounts, in both plants and animals. Much of the interest in fluorine arises from the toxic effects it may produce. When fluorine compounds are ingested beyond certain limits, definite harmful effects and even death may result. Chronic effects of fluorine ingestion include structural changes in the teeth and bones, mottling of the enamel, loss of appetite, retarded growth, and decreased milk production. Some forms of fluorine are more toxic than others, and apparently some species are more susceptible to the harmful effects of fluorine than others. Chronic fluorine poisoning in animals is the subject of a comprehensive review by Peirce, and the fluorine problem in the feeding of livestock is covered in a recent report by Mitchell (1942).

There is evidence that fluorides in very small amounts will prevent dental decay or lower the incidence of it, and it has been suggested on this basis and other observations that fluorine should be classed as a dietary essential.

Selenium. This mineral element occurs in the soil in certain parts of the country to such an extent that plants grown on the soil absorb enough selenium to make them toxic to animals and perhaps to man. Selenium poisoning is a livestock disease of the Great Plains and Rocky Mountain regions. It may occur in practically all species of farm animals including poultry.

Selenium poisoning occurs in acute and chronic forms. The chronic form, known also as alkali disease, is characterized by dullness, lack of vitality, emaciation, atrophy of the heart and liver, anemia, erosion of the long bones, loss of hair, and sloughing of the hoofs. The toxicity of plants and their selenium content show a high correlation. Foods containing 5 to 40 parts per million are toxic. Selenium poisoning is covered in a bulletin by Moxon and a review by Moxon and Rhian.

WATER

Water is the most abundant substance in the animal organism, constituting two-thirds or more of the weight of the body and 70 per cent or more of the weight of protoplasm. The water content of cattle in relation to age is shown in Fig. 119. It will be observed that the water content of the fetus is very high and that it diminishes as the fetus increases in age. After birth the water content of the animal decreases, at first rapidly, and then gradually. Water is not only abundant in the animal organism, it is also very important; for a starving animal may lose nearly all its glycogen and fat, half of its body protein, and about 40 per cent of its body weight, and still live, whereas the loss of 10 per cent of its water causes serious disorders, and the loss of twice that amount causes death.

Water Income. The water income of the organism includes the water consumed through the ingestion of liquids and solid foods and the water arising from metabolism (oxidation, dehydration). While man and most domestic animals require a certain amount of water as such or in the form of liquids of high water content, there are many animals capable of living for long periods of time without access to water except that contained in the food or arising in metabolism. Prairie dogs can live for months on dry food and apparently without access to water; they depend chiefly on metabolic water. Sheep at pasture or on succulent food may live and grow for long periods without access to water. The water of their food and the water of metabolism suffice to meet their needs. The ability of camels to go without water for long periods of time is probably due more to water of metabolism than to stored water (Babcock). The hump of the well-nourished camel contains a large amount of fat, which is a rich source of metabolic water.

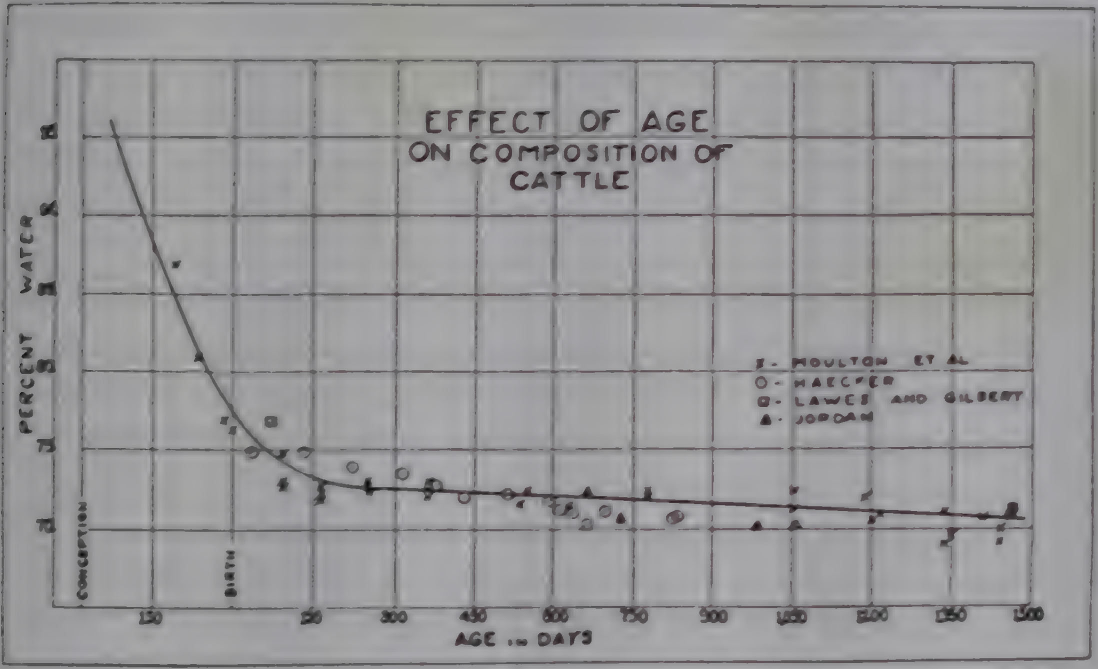


Fig. 119.—The relation between the water content of cattle and age. (From Armsby and Moulton's *The Animal as a Converter of Matter and Energy*, published by the Chemical Catalog Company, Inc.)

Water Outgo. The paths of water elimination are the kidneys, skin, lungs, and bowel. The relative amounts lost through these channels vary greatly in different species and in different individuals. Many factors are concerned in determining the water loss by each channel (Rowntree). The loss through the kidneys and the loss through the skin in the form of sweat are the most variable, and in general these losses stand in inverse relation to each other. The insensible water loss (skin and lungs) is apparently not a means of water regulation but is directly related to the rate of metabolism.

Metabolic Water. Water of metabolism is derived from the intracellular oxidation of organic substances containing hydrogen and from reactions of a dehydrative character such as the conversion of glucose into glycogen. It may be calculated that upon oxidation 100 gm. of fat yield 107.1 gm. of water; 100 gm. of starch, 55.5 gm. of water; and 100 gm. of protein, 41.3 gm. of water (Rowntree). It is evident that fat oxidation is a particularly rich source of metabolic water. Intracellular metabolic water causes a reduction of the molecular concentration within the cell, so that there is a movement of nutrient material from the intercellular spaces to the interior of the cell. Metabolic water is therefore of great consequence in cell nutrition, and its function cannot be assumed by water from an external source (Babcock).

Functions of Water. The great importance of water in the body may be judged from the foregoing statements. Its functions may be summarized as follows: (1) It is a necessary part of protoplasm. (2) It is a medium for the transfer of dissolved nutrients to the cells and for the removal of waste products from the cells. (3) It is concerned in the broad aspects of secretion, transport, and excretion. Thus the digestive juices are largely water; the mediums of transport (blood, lymph, cerebrospinal fluid) contain more than 90 per cent of water; urine and sweat are mainly water. (4) It is concerned in temperature regulation in the body. (5) It is a lubricant to body surfaces such as the joints, eyes, pleurae, pericardium, and peritoneum.

For further information on the significance of water in the animal body, the portions of this book devoted to blood, lymph, digestion and absorption, urine and sweat secretion, energy metabolism, and heat regulation may be consulted.

A recent review on water exchange is that of Peters. Summaries of recent literature on water metabolism have been made by McQuarrie and Adolph. The water economy of farm animals is reviewed by Leitch and Thomson.

VITAMINS

Vitamins are organic food substances which are required only in small amounts but which are necessary for the well-being or even the life of the animal. The study of vitamins is comparatively new, although deficiency diseases, which are caused in a number of instances by lack of vitamins, have long been recognized. During recent years rapid progress has been made in the chemistry of the vitamins, and much has been learned about their physiological actions.

In considering whether a vitamin is required by a certain species of animal, one should distinguish between the necessity for the vitamin in the metabolic processes and the necessity for the vitamin in the diet. For example, it is undoubted that ruminants require in their metabolic processes many of the members of the B-group of vitamins; however, ruminants do not have a dietary need for these vitamins, because they are synthesized by bacterial action in the rumen. Ascorbic acid, or vitamin C, is known to be required in the metabolic processes of many species. However, it is a dietary essential only in a limited number of species (man, monkey, guinea pig), for most species are able to synthesize it in their bodies in adequate amounts.

The first need might therefore be termed the physiological or metabolic need for the vitamin, the other the dietary or practical nutritional need. In the practical feeding of farm animals, other than poultry, vitamins A and D appear to be the only ones that need usually be considered, and under favorable feeding conditions even these are not likely to be deficient. The need for the other vitamins is usually adequately met by the presence of vitamins in the diet or by their synthesis in the animal. Solar radiation may supply a sufficient amount of vitamin D.

It is beyond the scope of this book to give an extensive discussion of the vitamins, either from the standpoints of the practical feeding of animals or of the pathological and clinical manifestations that occur in vitamin deficiencies. The books by Maynard and Udall and the National Research Council reports mentioned on p. 505 will give the reader further information on vitamins as related to farm animals. For vitamins in the nutrition of the dog, the book by McCay should be consulted. For yearly summaries of the general literature on vitamins, see the different volumes of the *Annual Review of Biochemistry*.

Vitamins may be conveniently divided into fat-soluble and water-soluble groups. The fat-soluble vitamins are vitamins A, D, E, and K. The water-soluble ones include thiamine, riboflavin, nicotinic acid or niacin, pyridoxine, pantothenic acid, biotin, folic acid, choline, inositol, and ascorbic acid. All of these except ascorbic acid belong to the vitamin B-complex. The evidence indicates that other water-soluble vitamins probably exist, but they have not yet been satisfactorily identified.

Vitamin A. This is a nearly colorless primary alcohol having the empirical formula, $C_{20}H_{29}OH$. It is found most abundantly in the fish-liver oils, egg yolk, liver, butter, cream, whole milk, kidney, and other animal products. Meat (muscle) contains little or no vitamin A. Another form designated as vitamin A_2 has been found in the oils obtained from some fresh-water fish. It is less active in promoting the growth of rats than is vitamin A_1, the form generally designated as vitamin A.

Foods of plant origin do not contain vitamin A but many of them contain instead yellow pigments from which the vitamin can be formed in the animal body. Three of these pigments are carotenes, alpha, beta, and gamma, and the other is the closely related compound cryptoxanthin. These substances, known as provitamins, can be converted to vitamin A in the liver. Some animals do not convert all the provitamin of their foods into vitamin A but store some of the provitamin as such. Different breeds of cows differ in their ability to convert carotene into vitamin A. Cows giving the yellower milks secrete more carotene and less vitamin A than those giving the paler milks. However the vitamin-A values of the milks are the same if the totals of carotene and vitamin A are the same. Colostrum is generally rich in vitamin A, but the amount present varies with the amount in the diet. The vitamin-A content of colostrum is important, for calves at birth are usually deficient in vitamin A. Following the intake of colostrum there is a definite increase in the vitamin-A content of the blood (Moore and Berry).

In the plants the carotenes occur closely associated with chlorophyll. Hence the leafy plants have a high vitamin-A value. In general, the greener the plant the higher is the carotene content.

Vitamin A and its precursors are rather easily oxidized. Therefore roughages lose a great deal of their vitamin-A value in field-curing and in storage.

So far as is known, all animals require vitamin A in the diet. The need is most noticeable in young animals, which, lacking the vitamin, fail to grow and finally die. Mature animals withstand lack of vitamin A for a long time. This indicates storage powers. The vitamin-A reserves of range cattle become depleted in 45 to 268 days when the animals are placed on a carotene-free diet (Riggs). The reserves of a well-fed dairy cow may last for months.

A most important function of vitamin A in the animal body is to maintain the health and functional integrity of epithelial structures. Changes in epithelial tissues in vitamin-A deficiency occur in many situations in the body and have been demonstrated in animals of many species and of all ages. The epithelial changes may be summarized as follows (Wolbach and Bessey): "atrophy of the epithelium concerned, reparative proliferation of basal cells, and growth and differentiation of the new products into a stratified keratinizing epithelium." Regardless of where the affected epithelium is located, the replacement epithelium is comparable with epidermis. As a rule the epithelial cells that are involved in vitamin-A deficiency have a secretory as well as a protective function, and are themselves without power to divide. Following are some of the locations in which epithelial changes occur in vitamin-A deficiency: salivary and buccal glands, respiratory tract, urogenital tract, eyes and associated structures. Since in vitamin-A deficiency the final epithelial product is the same, namely, a keratinizing epithelium, it is assumed that vitamin A is normally concerned in maintaining the structural and functional differentiation of this type of epithelial cell. The damaged epithelium is open to infections, which often follow. If vitamin A is administered and recovery occurs, the epithelium in the various locations returns to its original form and functions.

Vitamin A functions also in certain photochemical changes occurring in the retina in vision under low intensities of illumination. The rods, the retinal receptors concerned in dim-light vision, contain the pigment rhodopsin or visual purple. When exposed to light, rhodopsin breaks down into visual yellow, which is a mixture of the pigment retinene and protein. In the dark the reaction reverses and rhodopsin is re-formed. The change from rhodopsin to visual yellow is rapid; the reverse change is slower. These changes are believed to be the photochemical basis of dark and light adaptation. Visual yellow undergoes another reaction, which is the very slow transformation to visual white, a mixture of vitamin A and protein. Visual white can be changed to rhodopsin. During the reactions in the retina some of the vitamin A or retinene is lost and is replaced by vitamin A from the blood. If the blood level of vitamin A is too low, a functional night blindness will result.

Nervous lesions and symptoms occur in vitamin deficiency, especially in young animals. A possible explanation is that skeletal growth becomes retarded in young vitamin-A-deficient animals but the central nervous system and other soft organs continue to grow for a time. The continuing growth of the central nervous system in a nongrowing bony framework results in mechanical pressure on, and distortions and herniations of, the central nervous system. Structural and functional changes in the nervous tissue follow. Another possibility is that actual malgrowth of the bony structures occurs.

The effect of avitaminosis A has been extensively studied in cattle. Night blindness is one of the first clinical manifestation of vitamin-A deficiency. Convulsions, total blindness, and degenerative changes in the kidneys are later manifestations. Abortions and the birth of weak calves have been noted under natural conditions of vitamin-A deficiency

(Guilbert and Hart, Hart). The disease in cattle commonly known as cottonseed meal poisoning is primarily a deficiency of vitamin A (Halverson and Sherwood; Schmidt, 1941). Calves on diets low in carotene develop night blindness, papillary edema, permanent blindness associated with constriction of the optic nerve, and elevated cerebrospinal fluid pressure (Moore; Moore and Sykes). Studies of the levels of vitamin A and carotene in the blood plasma of cows and calves have been made by a number of investigators.

Studies on vitamin-A deficiency in horses have been made (Howell, Hart, and Ittner). "Night blindness, lacrymation, keratinization of the cornea, respiratory symptoms, reproductive difficulties, capricious appetite, progressive weakness, and death occur quite regularly." Vitamin-A deficiency is not the cause of joint lesions in the horse (Hart, Goss, and Guilbert). Histological changes in the retinas of horses showing vitamin-A deficiency have been studied (Andersen and Hart).

In sheep vitamin-A deficiency results in night blindness, nervous disorders, and reproductive troubles.

In pigs the absence of vitamin A results chiefly in nervous symptoms such as unsteady gait, incoordination, trembling of the legs, spasms, and paralysis. These animals have to be kept on a vitamin-A-deficient diet for several months before symptoms develop. Eye lesions are seldom present (Hughes, Aubel, and Lienhardt). In the experimental studies of Lund on vitamin-A deficiency of the pig, the symptoms were entirely of nervous origin. Several other workers have reported nervous symptoms in pigs on a vitamin-A-deficient diet. Other troubles are night and day blindness and dead, weak, or malformed offspring.

In avitaminosis A in the dog, xerophthalmia, corneal changes, nervous disturbances, and bone malformations are seen.

Vitamin-A deficiency in the fox is characterized mainly by nervous disorders. In some cases eye lesions, widespread epithelial changes, and degenerations in the nervous system are seen (Smith, 1942).

In chickens lack of vitamin A in the diet causes slower growth, lowered resistance to disease, failure of the glandular secretions, eye lesions, muscular incoordination, and other symptoms (Norris).

The mobilization of vitamin A from the stores in the liver is brought about by action of the sympathico-adrenal mechanism (Young and Wald).

Vitamin D. Several distinct forms of vitamin D are recognized, but two are of greatest practical importance. "These are activated ergosterol and activated 7-dehydrocholesterol. Other forms undoubtedly contribute to the total antirachitic effectiveness of certain agents, and it may be that the importance of some is greater than now appears. But for practical purposes, one may consider that all antirachitic medicines and foods owe their peculiar property chiefly to either or both of the two forms mentioned" (Bills). Activated ergosterol is also known as calciferol or vitamin D_2 and activated 7-dehydrocholesterol as D_3. Most antirachitic agents owe their antirachitic properties to vitamin D_3. No vitamin D_1 is recognized. The precursors of vitamin D, provitamins, are activated by exposure to ultraviolet radiation. The changes produced in the provitamins by irradiation involve a rearrangement of groups within the molecule.

The distribution of vitamin D in nature is very limited. Living plant tissue contains none. Some plant tissues when no longer living will, under the influence of sunlight, acquire considerable vitamin-D potency because of the activation of ergosterol. Properly cured hay, especially legume hay, contains a significant amount of vitamin D. Seeds and their by-products contain practically none. Natural foods containing vitamin D are of animal origin. Fish oils are rich natural sources. Egg yolk is a good source, and butter fat and meat products contain some of the vitamin.

Vitamin D is necessary for the prevention or cure of rickets. However the requirements of the different species for the vitamin vary greatly. Most animals carry only small reserves.

Rickets is a disease of the growing bones characterized by their failure to deposit proper amounts of tricalcium phosphate because of a lowering of the inorganic phosphorus, and, to a lesser extent, the calcium, of the blood. In rickets the inorganic environment in the growing bone is unfavorable for the necessary mineral deposition required in bone growth. A sufficient concentration of the bone-forming compounds in the blood is essential for their deposition, and this concentration is inadequate in rickets. Bone formation is in some way related to the enzyme phosphatase which occurs in large amounts in cartilage. In rickets there is an increase of the phosphatase content of the blood and bones.

Apparently vitamin D is required by all higher vertebrates, but under practical conditions it is necessary to add it to the diets of only those animals that do not have ready access to sunlight, especially during pregnancy and growth. With adequate exposure to sunlight, sufficient vitamin D is formed in the skin to meet the vitamin-D requirements of the animal. The provitamin in this case is 7-dehydrocholesterol (provitamin D_3), which can be synthesized in the body. Ultraviolet radiation from artificial sources is quite effective in protecting young animals from rickets. Krauss and Knoop have investigated this phase with calves both as to the duration of the irradiation and the skin regions giving satisfactory results.

Rickets may occur under practical conditions in chickens, pigs, calves, foals, and dogs. Clinical rickets in a calf is illustrated in Fig. 120. McCay has discussed rickets and the vitamin-D requirements of dogs.

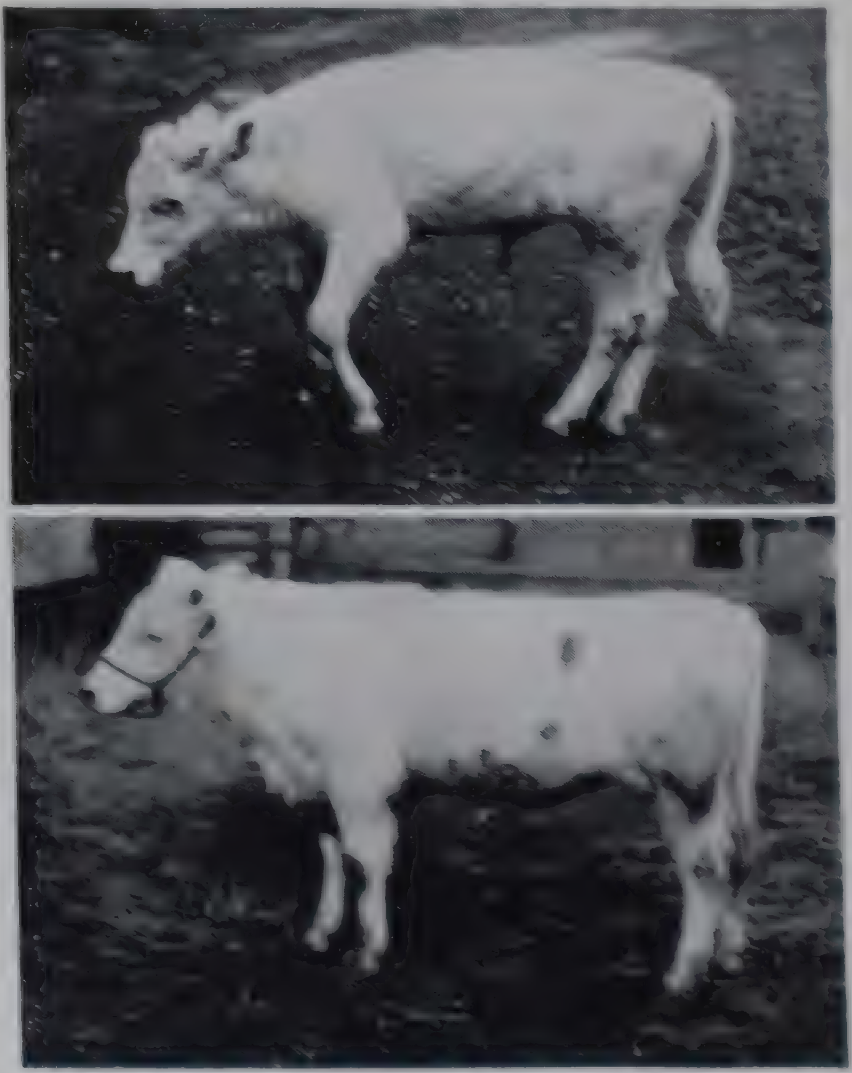


FIG. 120.—Calf suffering from clinical rickets (above). The same calf after having been on a rachitic diet and a vitamin-D supplement for six months (below). (From Rupel, Bohstedt, and Hart. *Wisconsin Agricultural Experiment Station Research Bull.* 115, 1933.)

The mode of action of vitamin D is not fully known. Its main action appears to be to increase the absorption of calcium by increasing the permeability of the intestine to calcium salts. The resulting increase in the serum calcium level leads to decreased parathyroid activity and thus to decreased phosphate excretion by the kidney. There is also evidence that vitamin D is concerned in the intermediary metabolism of the bone-forming elements. The view that vitamin D functions to promote the absorption of calcium from the alimentary canal and to aid in the mineralization of bone has received support in recent tracer experiments in which radioactive isotopes of calcium and strontium were administered to rachitic rats (Greenberg).

Vitamin E. Three naturally occurring forms of vitamin E are recognized: alpha-tocopherol, beta-tocopherol, and gamma-tocopherol. The first possesses the greatest vitamin activity. Synthetic alpha-tocopherol has the physical, chemical, and physiological properties of the naturally occurring substance. It is now available in large quantity.

Vitamin E is widely distributed in nature. The oils obtained from seeds contain large amounts, green leaves considerable amounts, animal tissues limited amounts.

That vitamin E is required for reproduction in rats has been known for a good many years. Absence of the vitamin from the diet causes sterility in animals of both sexes. In the male there is testicular atrophy, destruction of the germ cells, and finally destruction of the seminiferous epithelium. In female animals death and resorption of the developing young is a characteristic feature. If treatment is begun in time, the sterility resulting from lack of vitamin E can be cured by feeding the vitamin. Absence of vitamin E from the diet causes reproductive failure in chickens, both sexes being affected. To what extent vitamin E is required for reproductive activities in farm animals is at present uncertain. Apparently the goat neither requires it in the food (Thomas and Cannon) nor synthesizes it in significant amounts in the body (Underbjerg, Thomas, and Cannon). There is some evidence that swine require vitamin E for reproduction.

In any event, vitamin E is so abundant in naturally occurring foods that it ordinarily requires no attention in the practical feeding of farm animals.

Muscular Dystrophy. It has been shown in several species that the absence of vitamin E from the diet results in severe injury to the skeletal muscles—muscular dystrophy. The condition has been observed in puppies produced from dogs fed for long periods on a diet deficient in vitamin E (Anderson, Elvehjem, and Gonce). Injury to cardiac muscle may also occur. Nutritional muscular dystrophy of animals can be prevented or cured by the administration of alpha-tocopherol.

Recent work throws some light on the action of vitamin E in the prevention of muscular dystrophy. The affected muscle has a high rate of oxygen consumption, which can be reduced by the use of tocopherols. The latter are antioxidants and it is suggested that they reduce oxygen consumption in the dystrophic muscle by reason of this property. It also appears that the antioxidant action of vitamin E might be of value in protecting carotene and vitamin A from oxidation both in the alimentary tract and in the cells. These substances are destructively oxidized in the presence of unsaturated fats (*Nutrition Reviews*, 1946, 4, 324). Vitamin E might function to prevent or lessen this effect.

A nutritional muscular dystrophy in lambs known as stiff-lamb disease occurs under practical conditions. At autopsy gross and microscopic lesions have been found in the skeletal muscles of stiff lambs. Some of the animals show heart lesions. Recent studies by Willman and co-workers indicate that this condition can be prevented by feeding alpha-tocopherol to the ewes or to the lambs and that it can be cured by injecting a preparation of alpha-tocopherol into stiff lambs or by feeding it to them. It thus appears certain that a lack of vitamin E in the ration of lambs is the cause of stiff-lamb disease.

Functional and structural changes in the heart have been observed in cattle on vitamin-E-free rations (Gullickson and Calverley).

Vitamin K. At least two forms of this vitamin occur in nature, K_1 and K_2. Their composition is known and synthesis has been accomplished.

Vitamin K occurs especially in green leaves of plants. Dried alfalfa is a good source. The vitamin can be synthesized by several kinds of bacteria. Egg yolk and liver contain significant amounts. The vitamin is widespread in its occurrence.

Vitamin K is necessary for the formation of prothrombin in the liver. The mechanism of this action is not clear. In the absence of the vitamin the level of the prothrombin in the blood is reduced, the clotting power is impaired, and a hemorrhagic tendency develops. Vitamin K is therefore referred to as the antihemorrhagic vitamin. Birds and mammals of several species including man have been shown to develop this tendency to bleed in the absence of vitamin K or when its absorption from the intestine is defective. The presence of bile in the intestine is necessary for the absorption of vitamin K. Therefore when bile is excluded from the intestine by ligation of the bile duct, biliary fistula, or obstructive jaundice, failure of absorption of vitamin K occurs and a tendency to bleed develops. This happens even though there is ample vitamin K in the diet. In liver damage, bleeding may develop. For the action of vitamin K in sweet-clover disease, see p. 60.

Vitamin K can be formed by bacterial action in the intestine of many animals and in the rumen (McElroy and Goss). This fact, together with the rather wide distribution of the vitamin in foods, indicates that avitaminosis K is not an important practical problem in the feeding of animals. Vitamin K is the subject of a review by Almquist (1941).

Thiamine. This is also known as vitamin B_1. Its chemical identity is known and it is now available synthetically in large quantity. Brewer's yeast is a very rich source of thiamine. It is abundant in the germs of seeds, and is present in fair amounts in the leaves of plants. Good hay contains significant amounts. Egg yolk, heart, liver, and kidney are important sources. Milk is not a rich source of thiamine.

Thiamine, along with other members of the vitamin B-complex, occurs in all living cells where it is required in the metabolic processes. Since animals are unable to synthesize thiamine, it must be present as a part of the diet of all species unless there is bacterial synthesis of the vitamin in the alimentary canal.

Ruminants do not require thiamine in the food, for this vitamin and other members of the B-group are synthesized in the rumen. This has been amply demonstrated by the work of a number of investigators (McElroy and Goss; Wegner, Booth, Elvehjem, and Hart; Hunt and co-workers; and others). The question has frequently arisen as to whether young ruminants require a dietary source of thiamine and the other members of the B-group of vitamins. A complete answer is not available. Until the rumen develops and bacterial action becomes well established, it appears probable that a dietary source of the B vitamins is required. In general it may be said that after the calf is about two months old, rumen synthesis of the B vitamins is satisfactory. Should conditions occur under which the substrate in the rumen is unsatisfactory for bacterial growth, it is probable that an outside source of the B vitamins would be required. This might be true in animals receiving an improperly balanced ration and in sick animals. Little precise information on this point is available.

Thiamine functions as a catalyst in the metabolic processes. After undergoing phosphorylation in the cells, it unites with a specific protein to form the enzyme carboxylase. This enzyme is concerned with the metabolism of keto acids, particularly the oxidation of pyruvic acid.

In man the disease beriberi is caused by a deficiency of thiamine and possibly other factors in the diet. It is characterized by degenerative changes in the nervous system. In birds the disease polyneuritis is caused by a lack of thiamine. There are loss of appetite, emaciation, and disorders of the central nervous system. Convulsions, paralysis, and death occur unless thiamine or thiamine-containing foods are given. In dogs there is lack of appetite, poor growth, muscular weakness, and polyneuritis characterized by nerve degeneration, ataxia, and paralysis. In pigs thiamine deficiency results in loss of appetite, vomiting, respiratory difficulties, and great weakness. Bradycardia is usually present and acute cardiac failure may terminate the condition. Electrocardiographic changes, attributable at least in part to vagus overaction, are seen. The underlying metabolic disturbance in thiamine deficiency is believed to account for the functional changes in the heart. No neurological symptoms nor degenerative changes in the nervous system are evident in thiamine deficiency of the pig (Wintrobe and co-workers, 1942, 1943a). In foxes the condition known as Chastek paralysis is essentially a thiamine deficiency. Foxes fed uncooked fish develop the condition because an enzyme in the fish (thiaminase) destroys thiamine in the digestive tract. The condition can be prevented or cured by adding thiamine to the diet.

Owing to the widespread presence of thiamine in common foods and to the synthesis of thiamine in the rumen, thiamine deficiency is ordinarily no problem in the feeding of farm animals including poultry. In the human diet thiamine is likely to be deficient.

Riboflavin. This vitamin, known also as vitamin B_2 or G, consists of a ribose sugar combined with flavin. The compound has been prepared synthetically. Riboflavin is abundant in milk, egg white, liver, and green leaves. Heart, pancreas, muscle, kidney, brain, and other organs contain it. It is present in grains and legumes. It is destroyed by oxidation and light.

Riboflavin probably is required in the metabolic processes of all animals. However it is not a dietary requirement in ruminants, for in these animals the vitamin is synthesized by bacterial action in the rumen. The question naturally arises as to whether the horse is able to synthesize the B vitamins in adequate amounts in the alimentary canal. Studies have been made for several members of the B-group. So far as riboflavin is concerned, the evidence indicates that intestinal synthesis is not adequate to meet the horse's requirement for this vitamin and that a dietary source is necessary (Pearson and co-workers).

Riboflavin is concerned in the physiological oxidations. It is required as the coenzyme in the manufacture of the yellow enzymes, of which there are some twelve or more.

A lack of riboflavin in chicks results in failure to grow, paralysis, and death. Poor hatchability and high mortality of the embryo are seen in mature chickens. Dogs fed diets lacking in riboflavin collapse and suddenly die in 6 to 8 weeks (Axelrod and co-workers). Riboflavin is required for hemoglobin production in the dog (Spector and co-workers). Riboflavin deficiency in pigs is characterized by slow growth, a crippled condition, corneal and lens opacities, normocytic anemia, changes in hair, skin, and hoofs, collapse and death (Hughes, 1939; Patek, Post, and Victor; Wintrobe and co-workers, 1944).

A deficiency of riboflavin in the diets of animals under practical conditions is not known to occur. There is some evidence that riboflavin deficiency may be concerned in periodic ophthalmia in horses (Jones, Maurer, and Roby). Since ruminants synthesize riboflavin in the rumen, the vitamin need not be considered in the practical feeding of these animals.

Nicotinic Acid (Niacin). Nicotinic acid or nicotinic acid amide (also compounds capable of yielding these substances in the body) functions as a vitamin, being required for the growth and functioning of all cells of higher animals. It is present in many foods of animal and plant origin.

It has been shown that the fowl, dog, fox, cat, pig, monkey, and man require nicotinic acid in the diet and develop deficiency symptoms when it is lacking.

Nicotinic acid amide is necessary for the synthesis of codehydrase I and codehydrase II and is therefore concerned in the physiological oxidations.

In the dog nicotinic acid is effective in preventing and curing the deficiency disease known as blacktongue. This was first shown by Elvehjem and co-workers. Other investigators have confirmed their findings. Blacktongue has long been recognized in dogs, especially in the South. Some of the manifestations of the disease are lack of appetite, loss of weight, reddening and ulceration of the mucous membrane of the mouth and tongue, diarrhea, and death. A deficiency disease of cats has been described which responds to the administration of nicotinic acid (Heath, MacQueen, and Spies).

Swine require nicotinic acid in the diet. Nicotinic acid deficiency has been reported in pigs under farm conditions (Madison, Miller, and Keith).

Ruminants can synthesize nicotinic acid in the rumen, probably by bacterial action (Winegar, Pearson, and Schmidt; Wegner, Booth, Elvehjem, and Hart). Recent work suggests that the calf is capable of synthesizing niacin in its tissues.

Nicotinic acid is synthesized in the body of the horse and is therefore not required in the diet (Pearson and Luecke).

Lack of nicotinic acid in the diet of man causes pellagra.

Recent work shows that nicotinic acid and tryptophane are in some way interrelated in metabolism. Apparently tryptophane exerts a sparing action on, or in some way substitutes for, nicotinic acid. The relationship of nicotinic acid to tryptophane in the nutrition of the pig has recently been studied by Luecke and co-workers.

Pyridoxine. This substance, also known as vitamin B_6, is a pyridine derivative. It has recently been prepared in synthetic form. The emprical formula is $C_8H_{11}NO_3$. It is found in yeast, lean meat, kidney, milk, molasses, legumes, cereals, wheat by-products, and other foods.

Rats fed a diet lacking in pyridoxine develop a characteristic dermatitis. Severe anemia and cardiac dysfunction occur in dogs on a pyridoxine-deficient diet (Street and co-workers). Chickens lacking pyridoxine eat little, grow slowly, and develop nervous disturbances that may lead to convulsions and death. Turkeys show similar signs and symptoms in pyridoxine deficiency. Pigs require pyridoxine in the diet. Pyridoxine-deficient swine show severe anemia, epileptiform convulsions, and fatty infiltration of the liver (Wintrobe and co-workers, 1943b). Ruminants synthesize pyridoxine in the rumen, but young calves on a restricted diet and cows with open rumen fistulas may develop poikilocytosis, a condition in which abnormal red cells are found in the blood. Pyridoxine or yeast is effective in the treatment of the condition (Reid, Huffman, and Duncan). Probably under the conditions mentioned rumen synthesis of pyridoxine is inadequate.

Pyridoxine is concerned in the intermediary metabolism of protein and apparently in fat metabolism.

Pantothenic Acid. The chemical formula of this substance is now known and it has been prepared synthetically. As the name implies pantothenic acid is widely distributed in nature. It has been shown to be a dietary essential in a number of species, including, apparently, the horse. It is synthesized in the rumen. Its specific role in metabolism is not yet clear.

In chicks pantothenic acid deficiency results in retarded growth and the development of a pellagralike syndrome. At autopsy liver damage and changes in the spinal cord are evident.

Pantothenic acid deficiency in the dog has been studied (Silber). In pups the appetite decreases, food intake is diminished, and growth retardation follows. Collapse occurs after two months. Older dogs are less affected by the absence of pantothenic acid from the diet. This may indicate a lower requirement for maintenance than for growth, or the utilization of stores of pantothenic acid already in the tissues, or synthesis in the intestine. The livers of pantothenic-acid-deficient dogs show an accumulation of fat.

In young pigs pantothenic acid deficiency results in diarrhea and other gastro-intestinal disturbances, severe growth impairment, respiratory symptoms, and an abnormal gait, associated with histological changes in the nervous system (Wintrobe and co-workers, 1943c). It has been suggested that the "goose-stepping" gait frequently seen in swine herds on the farm may be evidence of pantothenic acid deficiency (Hughes and associates).

Biotin. The composition of this substance is now known and it is available in pure form. It is identical with coenzyme R. Knowledge of the distribution of biotin in nature is not exact. Yeast and liver contain large amounts, which fact indicates the close relationship of biotin to the B-group of vitamins. Many other substances have been shown to contain varying amounts of biotin. Its universal distribution in living cells suggests that it has basic physiological importance, but its function is unknown.

Biotin is a dietary essential for many species. It is synthesized in the rumen. In chicks and poults biotin deficiency is a factor in the production of perosis (p. 515). Dogs develop a progressive paralysis on a biotin-free diet. The condition is alleviated by biotin in small doses (Smith, 1945).

The feeding of dried egg white to experimental animals results in a deficiency known as egg-white injury. This is now known to be a biotin deficiency. A substance in egg white known as avidin combines with biotin in the digestive tract to form the unabsorbable avidin-biotin complex. Avidin is a protein substance which occurs in certain living tissues, and its affinity for biotin might have metabolic significance in these locations.

Our knowledge of biotin and the avidin-biotin complex has recently been reviewed by Hertz.

Folic Acid. This member of the vitamin B-complex has recently been isolated and synthesized. The synthetic product has been designated as pteroylglutamic acid. Folic acid is widely distributed in nature as folic acid conjugate. It may be of fundamental importance in cell metabolism. Folic acid is in some way related to the erythrocyte-maturing factor (p. 31), if it is not actually a part of it. It has proved successful in the treatment of pernicious anemia and sprue in man. Folic acid metabolism is a field of very active research, and it may be expected that the relation of folic acid to the erythrocyte-maturing factor will be clearer in the near future.

Folic acid is required by the chick for normal growth and hemoglobin formation, and it stimulates hemoglobin production in hens made anemic by bleeding. Folic acid is probably required by other species.

Choline. This substance is now often regarded as a vitamin and it is sometimes placed with the B-group of vitamins. However objections have been raised to both of these points of view, particularly the latter (McHenry and Patterson). Choline is required in the body for the formation of acetylcholine and the phospholipids. Choline, together with methionine, cystine, and other substances, participates in the metabolic process known as *transamination*. Methionine or betaine can give a methyl group for the synthesis of choline, and the latter can contribute a methyl group for the formation of methionine. There is therefore some synthesis of choline in the body, and it appears that some animals are able to meet their entire need for choline in this way. Since, however, choline, or a choline precursor is a dietary essential under some conditions and in some animals, it is usually classed as a vitamin. When choline is lacking in the metabolic processes, fat accumulates in the liver, persumably because the synthesis of lecithin cannot take place in the absence of choline. When choline is added to the diet, the fat accumulation disappears. A substance which prevents or cures this abnormality of fat metabolism is said to be a *lipotropic factor* (p. 475). Other lipotropic factors are lipocaic and *inositol*, the latter being sometimes classed as a vitamin. It occurs in certain phospholipids and presumably owes its lipotropic action to its participation in their formation.

Choline is a dietary need for poultry. In its absence chicks and poults show growth retardation and perosis (p. 515).

Puppies may develop fatal choline deficiency on a choline-free diet in less than three weeks. Fatty infiltration of the liver is the characteristic postmortem finding.

Choline is a dietary essential for the rat and the rabbit.

Farm mammals are not known to require choline in the diet. Even if it is a dietary essential, it is likely that ordinary rations supply enough.

Ascorbic Acid. This substance is known also as vitamin C. The empirical formula of ascorbic acid is $C_6H_8O_6$. It has been prepared synthetically. Synthetic ascorbic acid is as effective physiologically as the naturally occurring substance.

Fresh fruits and fresh vegetables are the principal sources of vitamin C. In general, animal products contain little of the vitamin. Grains and hays do not contain it. Vitamin C is easily destroyed by oxidation and light.

Absence of vitamin C from the diet produces scurvy. Man, the other primates, and the guinea pig are the only animals known to be susceptible to scurvy. The other animals are capable of synthesizing ascorbic acid in their bodies, in most cases in amounts sufficient for their needs. Dairy cows are not dependent on a dietary source of vitamin C (Wallis; Vavich and co-workers). When kept for several years on experimental rations low in vitamin C, they show normal concentrations of vitamin C in the blood plasma and milk and give off in the feces, milk, and urine amounts of vitamin C far in excess of the intake. Evidently synthesis occurs somewhere in the body.

The metabolism of ascorbic acid in the horse has been studied by Pearson, Sheybani, and Schmidt. When ascorbic acid is given by mouth to the horse, much of it is destroyed in the alimentary tract.

Rasmussen, Cole, and Miller have studied the carotene, vitamin-A, and ascorbic acid contents of mare's plasma. No correlation was evident between ascorbic acid and plasma vitamin-A contents.

Several reports in the literature have suggested that the synthesis of ascorbic acid by bovines may not always be adequate to meet their needs and that breeding performance and ascorbic-acid content of blood plasma may be correlated; but results obtained by other workers have failed to confirm these reports.

A relationship between ascorbic acid and periodic ophthalmia in horses has been suggested (Errington; Jones, Maurer, and Roby).

The function of ascorbic acid is to promote the formation and maintenance of intercellular materials. In scurvy these collagenous substances are lacking. The physiological mechanism whereby ascorbic acid aids the formation of intercellular substances is unknown (Wolbach and Bessey).

Chapter XXVII

HEAT REGULATION

POIKILOTHERMISM AND HOMOIOTHERMISM

VERTEBRATE animals may be divided into two great classes as regards the relation of the temperature of the body to that of the environment: poikilothermal or "cold-blooded" animals are those whose temperature varies directly with that of the environment, and homoiothermal (homeothermal) or "warm-blooded" animals are those whose temperature is largely independent of that of the environment. Mammals and birds are homoiothermal, whereas other animals are poikilothermal. Some mammals are homoiothermal only under conditions of favorable environmental temperature, becoming poikilothermal when the surrounding temperature is cold. Such animals hibernate when they are no longer able to compete with the cold.

Poikilothermal animals maintain a temperature not far from that of the environment. When the temperature of the surroundings falls, that of their bodies also falls; when the temperature of the surroundings rises, that of their bodies rises. The activities of such an animal, for example, a frog, are therefore markedly conditioned by the environmental temperature. In cold weather the animal passes into a deep sleep, whereas in hot weather it may burrow into the mud to keep cool.

Mammals and birds, homoiothermal animals, have, on the contrary, an elaborately developed heat-regulating device which enables them to maintain, under any ordinary conditions, a relatively constant body temperature regardless of the temperature of the surroundings. Such animals are, from this point of view, not mere creatures of the environment but are able to carry on their usual activities under a wide range of external temperature. From the standpoint of evolution, the warm-blooded condition is the more recently developed. Carnivores possess better regulation against overheating than do most herbivores. The reason for this probably lies in the fact that the latter animals do not have as mobile a water reserve and are therefore more dependent on radiation and conduction, than on the vaporization of water, for heat loss.

THE SEAT OF HEAT PRODUCTION

Heat is produced by oxidations in the active protoplasm of the body. Muscle and gland, making up the greater part of the active tissues, are therefore the principal seats of heat production, and since skeletal muscle occupies the larger place in this mass of protoplasm, one would expect to find this structure of first importance as a place of heat production. Experiments show, in fact, that something like 70 per cent of the heat of the body is produced in skeletal muscle. The liver, because of its active metabolism and large size, is next in importance in heat production. Evidently the amount of heat produced in a muscle or a gland is not the same at all times. It varies directly with the degree of activity of the structure.

BODY TEMPERATURE

The Normal Rectal Temperature. The body temperature of animals is usually determined by inserting a thermometer into the rectum. The rectal temperature is a fair index of the internal temperature of the body, although the temperature is not the same in all parts of the body, nor is it always the same in a given place. The temperature of the mouth is lower, and that of the surface of the body may be much lower, than that of the rectum.

The accompanying table shows the normal rectal temperatures of animals. Attention is called especially to the considerable intraspecific and interspecific variations in body temperature and to the higher temperature of the chicken. This higher temperature is an avian characteristic.

Gradients of Temperature. In man and animals there are gradients of temperature in the subcutaneous tissue and in the rectum, the lower temperatures being toward the exterior of the body. The temperature gradient in the rectum and the vagina of cattle has been studied by Kriss, who showed that the temperature when measured at a depth of 6 or 7 inches is decidedly higher than when measured at a depth of 4 or 5 inches. In one cow the following temperatures in the rectum were recorded within a few minutes of one another: at a depth of 4 inches, 100.5 degrees F.; 5 inches, 101.2; 6 inches, 101.4; 7 inches, 101.6.

Diurnal Variations. Many conditions are capable of causing normal variations in body temperature, among which may be mentioned age, sex, season, time of day, environmental temperature, exercise, eating, digestion, and drinking of water. Variations related to the time of day are designated as diurnal variations. The extent and time of such temperature changes vary somewhat in different species. In man the maximum temperature occurs in the early evening and the minimum in

RECTAL TEMPERATURES

Animal	Temperature				Author
	Average		Range		
	degrees F.	*degrees C.*	*degrees F.*	*degrees C.*	
Stallion	99.7	37.6	99.0–100.6	37.2–38.1	Fontaine
Mare	100.0	37.8	99.1–100.8	37.3–38.2	Fontaine
Beef cow	101.0	38.3	98.0–102.4	36.7–39.1	Hewitt (1920–21)
Dairy cow	101.5	38.6	100.4–102.8	38.0–39.3	Woolridge (cited by Hewitt)
Sheep	102.3	39.1	100.9–103.8	38.3–39.9	Clawson
Goat	103.8	39.9	101.7–105.3	38.7–40.7	Damant
Pig	102.5	39.2	101.6–103.6	38.7–39.8	Palmer
Dog	102.0	38.9	100.2–103.8	37.9–39.9	Friedman and Bennett
Cat	101.5	38.6	100.5–102.5	38.1–39.2	Hobday
Rabbit	103.1	39.5	101.5–104.2	38.6–40.1	Frothingham and Minot
Chicken (daylight)	107.1	41.7	105.0–109.4	40.6–43.0	Fronda

the early morning. In cows Kriss found the temperature to be practically constant in the morning and in the afternoon until about 2:30 P.M., from which time until about 5 P.M. it gradually rose. Gaalaas (1945) reports that the body temperature of the cow is regularly higher in the afternoon than in the morning irrespective of season or month. The average body temperature of Jersey cows is 101.1 ± 0.5 degrees F. (air temperature, 50 to 60 degrees F.; relative humidity, high). Diurnal variations in the body temperature of the hen are shown in Fig. 121.

THE REGULATION AGAINST OVERHEATING

Heat is being produced constantly in the body as a result of physiological oxidations. There must therefore be some provision for insuring a constant loss of heat; otherwise the temperature of the body would soon rise to such a height that life would no longer be possible. Heat is regularly lost from the body in the following ways: (1) radiation, conduction, and convection; (2) vaporization of water from the skin and respiratory passages; (3) excretion of feces and urine. The first two ways are much more important in heat dissipation than the last way, and their effectiveness is largely dependent upon an adequate water reserve in the body. The constitute the physical mechanism of heat loss (Barbour).

Radiation, Conduction, and Convection. *Radiation* is the transfer of energy across space without heating the space through which it passes. In the case of heat energy the transfer is effected by waves in the infra-red part of the electromagnetic spectrum. Upon striking a body the radiation may be absorbed, with a resulting rise in temperature of the body. *Conduction* is the passage of heat energy from particle to particle of matter by increased molecular agitation. *Convection* is the transfer of heat energy by a circulation of heated material (gas, liquid), which is less dense than the cooler material.

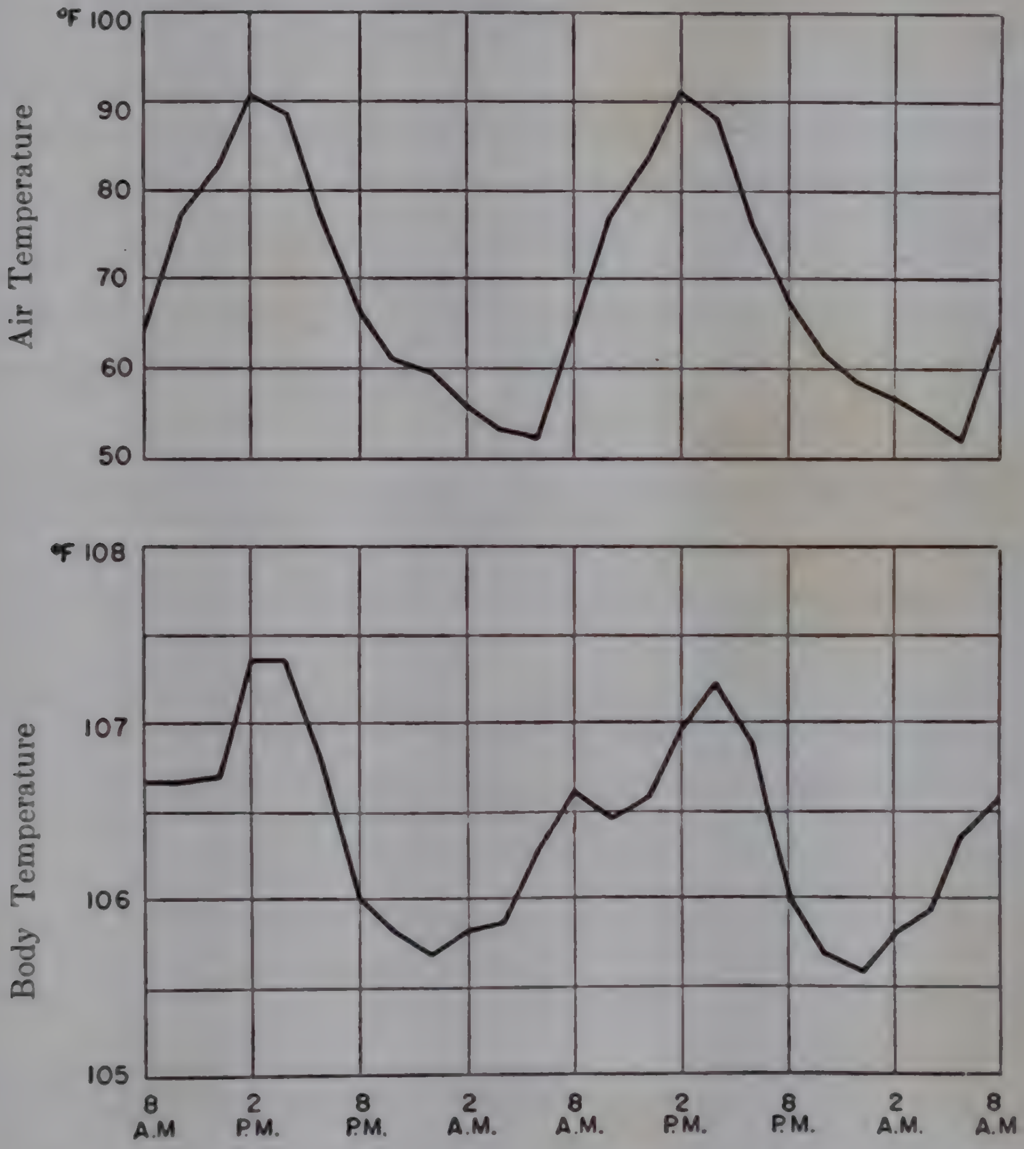


FIG. 121.—Diurnal variations in the body temperature of hens and the air temperature over a 48-hour period. The body temperatures are averages for a number of hens. Note that the hottest part of the day and the highest body temperature coincided, but not the coolest part and the lowest body temperature. (From Heywang, *Poultry Science*, 1938, 17.)

Under ordinary conditions about 75 per cent of the heat lost from the body is dissipated by radiation, conduction, and convection. Recent studies on man indicate that about 60 per cent of the heat is lost by radiation. The wavelengths of the infra-red radiations from the human skin vary from about 5 to 20 microns (Du Bois, 1937). Similar values would apply to animals since their temperatures are similar to man's temperature. The efficiency of radiation, conduction, and convection in heat loss is to a considerable extent conditioned by the external temperature. When this temperature becomes equal to that of the body, radiation, conduction, and convection cannot operate; when it rises above that of the body, they tend to warm the body instead of cool it. In the latter circumstance other means, mainly the vaporization of water, tend to prevent a rise of body temperature. In addition to radiation, conduction, and convection from the skin surface, conduction from the respiratory passages by the warming of inspired air must also be considered. This accounts for only a small amount (in the dog less than 3 per cent) of the heat lost by the general method of radiation, conduction, and convection.

The amount of heat lost by radiation, conduction, and convection is to a large extent controlled by the organism through the vasomotor nervous mechanism (Chapter VII). Vasodilatation in the skin causes a greater amount of warm blood to flow through this region, and if the external temperature is below that of the blood, heat loss is increased. Vasoconstriction, on the contrary, causes a decrease of heat loss through the skin. The vasomotor nerves are caused to function either by the reflex action of heat or cold on the skin or by the action of blood of slightly altered temperature in the central heat-regulating mechanism. Warmth, acting reflexly or by raising the temperature of the blood, causes the vasodilator mechanism to operate; whereas cold, acting reflexly or by lowering the temperature of the blood, causes the vasoconstrictor mechanism to function.

External temperature affects not only the distribution of blood but the concentration as well. Warmth tends to cause blood dilution, which favors heat loss. Cold tends to cause concentration of the blood. This favors heat conservation.

The heat loss by radiation, conduction, and convection is in some animals under a further control through the pilomotor nerves and muscles, which regulate the degree of erection of the hairs and the similar mechanisms that regulate the movements of the feathers in birds. Erection of hairs or ruffling of feathers, when the pilomotor muscles contract, entraps a thicker layer of still, moist air around the body and helps to conserve heat. On the contrary, when the hairs and feathers are less erect, heat loss is facilitated.

In animals that develop heat polypnea (rapid, shallow breathing caused by high external temperature), conduction from the lungs is increased somewhat during this condition. This control is vested in the respiratory nervous mechanism (Chapter X).

Vaporization of Water from the Skin and Lungs. Vaporization of water is an efficient way of cooling the body, the amount of heat lost from the body by the vaporization of one gram of water being approximately 0.58 Cal. Generally speaking, at ordinary temperature, about 25 per cent of the heat produced in resting mammals is lost by vaporization of water from the skin and respiratory passages. In the chicken the loss in this way is less: 12 to 25 per cent, with an average of about 17 per cent (Fig. 122). The water so eliminated is an insensible loss,

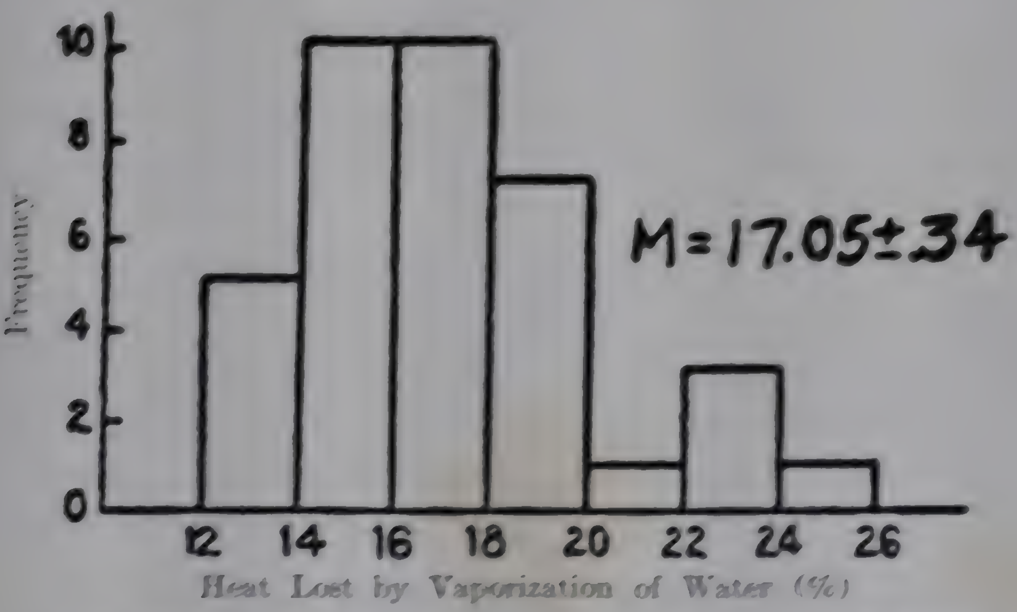


Fig. 122.—The percentage of heat lost by vaporization of water. Hens under basal conditions. (From Dukes, *Journal of Nutrition*, 1937, **14**.)

and it appears to be about as important in heat regulation in animals whose sweat mechanism is poorly developed (cow) or absent (rabbit) as in animals with a well-developed sweat apparatus (man, horse). At higher temperatures, however, the loss of heat by vaporization of water from the skin is much more efficient in animals with a well-developed system of sweat glands. Canines, more than other animals, have developed the ability to vaporize a large amount of water from the respiratory passages. When the external temperature is high, these animals show heat polypnea, which causes the vaporization of much water but which ordinarily causes little change in the gaseous composition of the blood. At times, however, there may be a marked reduction in the carbon dioxide content of the arterial blood.

The insensible water loss, cutaneous and pulmonary, under basal conditions is rather constant. However, if the skin temperature is increased, either by external heat or by an increased flow of blood through the skin, there will be an increase in the cutaneous insensible water loss, probably by diffusion through the outer layers of epidermis (p. 429). In animals that develop heat polypnea the pulmonary water loss increases with the environmental temperature and is under the control of the respiratory nervous apparatus. The loss of water through the sweat glands is under the control of the sweat nervous mechanism (Chapter XXI).

Leitch and Thomson have brought together a large amount of data on the heat loss by vaporization in cattle at different environmental temperatures and at various planes of nutrition. Newbergh and Johnston have assembled data on the percentage of heat lost by vaporization in a number of species.

Excretion of Feces and Urine. The excreta leave the organism at body temperature. They therefore occasion the loss of a small, usually negligible, amount of heat.

THE REGULATION AGAINST COOLING

When the temperature of the environment is reduced, some means must be taken by the warm-blooded animal to prevent a drop in its body temperature. This regulation against cooling is brought about first by a reduction of heat loss (the so-called physical regulation) and later by an increase of heat production (the so-called chemical regulation).

Reduction of Heat Loss. When the environmental temperature falls, the first compensation against a cooling of the body is effected through a reduction of heat loss. External cold causes vasoconstriction in the skin, and the resulting decrease in blood flow diminishes the loss of heat by radiation, conduction, and convection. The secretion of sweat, if in progress, is decreased. Erection of hairs or of feathers occurs. If the temperature of the environment continues to fall, there comes a time when the heat-conserving mechanisms are no longer able to prevent cooling, and heat production must be increased.

The external temperature at which the heat-retaining mechanisms are no longer able to maintain a constant body temperature and at which heat production has to be increased is known as the critical temperature. This varies a good deal in different animals (Chapter XXII). A well-developed heat-retaining ability betokens a low critical temperature. Man lowers his critical temperature, that is, increases heat retention, by covering his skin with clothes. Hair, fur, feathers, and thick layers of subcutaneous fat act similarly in animals. Among farm animals cattle and sheep have the lowest critical temperature and are therefore best able to withstand the cold. The critical temperature being lower in nonfasting than in fasting animals, the former are better able to withstand a low environmental temperature.

Increase of Heat Production. When the heat-retaining mechanisms have exerted themselves maximally in an effort to prevent a fall of body temperature, an increase in heat production begins if the surrounding temperature continues to fall. Since most of the heat of the body is produced in the skeletal muscles, one would expect to find these structures of first importance in the increased metabolic rate that accompanies the fall in environmental temperature. The principal way in which the increased metabolism is brought about is by shivering: rapid muscular contractions, which result in increased heat production. The question whether increased heat production can be called forth without shivering is one about which considerable controversy has existed. Experiments of Cannon and co-workers tended to show that exposure to cold increases the output of adrenaline and that this substance is capable of causing an increase in the metabolic rate in the absence of shivering. However, the more recent work of Hemingway and Hathaway on dogs shows that the increase of metabolic rate upon exposure to cold without acclimatization is caused largely by shivering. The nonshivering component of the increase was so small that it could have had little effect in combating exposure to cold under the conditions prevailing in the experiment. It is recognized that exposure to cold causes an increased output of the hormone thyroxine, but it takes some time for its effect to come on. It is quite possible, also, that the adrenal glands play a part in this slow upward adjustment of the metabolic rate upon prolonged exposure to cold. It appears, however, that the quick, emergency increase in heat production is accomplished mainly by shivering.

In so far as the increased heat production upon exposure to cold is brought about by shivering, it is under the control of the central nervous system through the motor nerves to the skeletal muscles. The nerve centers concerned are stimulated reflexly by the action of cold on receptors in the skin and directly by the action of blood of slightly lowered temperature reaching the centers. The endocrine component of the increase, when it occurs, is actuated by the factors that control the endocrine glands concerned, namely, the thyroid and possibly the adrenals.

Hemingway made observations on the onset of shivering in normal and anesthetized dogs in a cool environment (temperature, 22 degrees C.; relative humidity, 50 per cent). In the normal dog shivering began when the rectal temperature had fallen about 1 degree C. This required less than an hour. In dogs anesthetized with pentobarbital a fall in rectal temperature of about 3.5 degrees C. took place before shivering occurred. This required nearly three hours. The vasomotor responses to cold were also dulled by anesthesia.

SUMMARY OF THE NERVOUS REGULATION OF BODY TEMPERATURE

The regulation against a rise of body temperature is under the control of the nervous system through (1) the vasomotor center and nerves, (2) the sweat center and nerves, (3) the respiratory center and nerves; and (4) the pilomotor nervous mechanism.

The regulation against a fall of body temperature causes at first a reduction of heat loss by vasoconstriction in the skin, a decrease in the activity of the sweat glands, and erection of hairs or feathers. These changes are under nervous control. When they are no longer effective in preventing a fall of body temperature, an increase of heat production begins. This is under control through the motor nerves to the skeletal muscles.

THE CENTRAL CONTROL OF HEAT REGULATION

Heat regulation is developed only in those animals with a highly organized nervous system. A heat "center" with a thermostatlike action exists in the hypothalamus. Nuclei in the posterior part of the hypothalamus are concerned with heat retention and production, whereas nuclei in the anterior part are concerned with heat loss.

Evidence from a number of sources shows that the heat center is activated in two ways. The first way is through the temperature of the blood bathing the center. When the blood is cooled the center is stimulated, and body heat is conserved or more heat is produced; when the blood is warmed the center is depressed, and less heat is produced or more heat is lost. The second way in which the center is activated is through nervous reflexes from the skin; cold stimulates the center, heat depresses it. It is evident that the work of the heat center must, in the end, be carried out through the various nervous mechanisms previously described as being concerned in heat regulation: the vasomotor, sweat nervous, respiratory nervous, pilomotor, and skeletal motor mechanisms.

REACTIONS OF ANIMALS TO DIFFERENT ENVIRONMENTAL TEMPERATURES

A good deal of recent work involving the common species has been done and it is proposed to give some of this work separate consideration at this time. Most of the studies have been made on the effects of hot temperatures. The experiments of Lee and co-workers in Brisbane (see also Robinson and Lee) on the reactions of animals to hot atmospheres are comprehensive and include a number of species. The effects of different environmental temperatures on the rectal temperatures of the sheep, pig, dog, and fowl are shown in Fig. 123. A number of the observations made and conclusions drawn are of general interest but only a few can be given here. Anyone interested in the effects of high

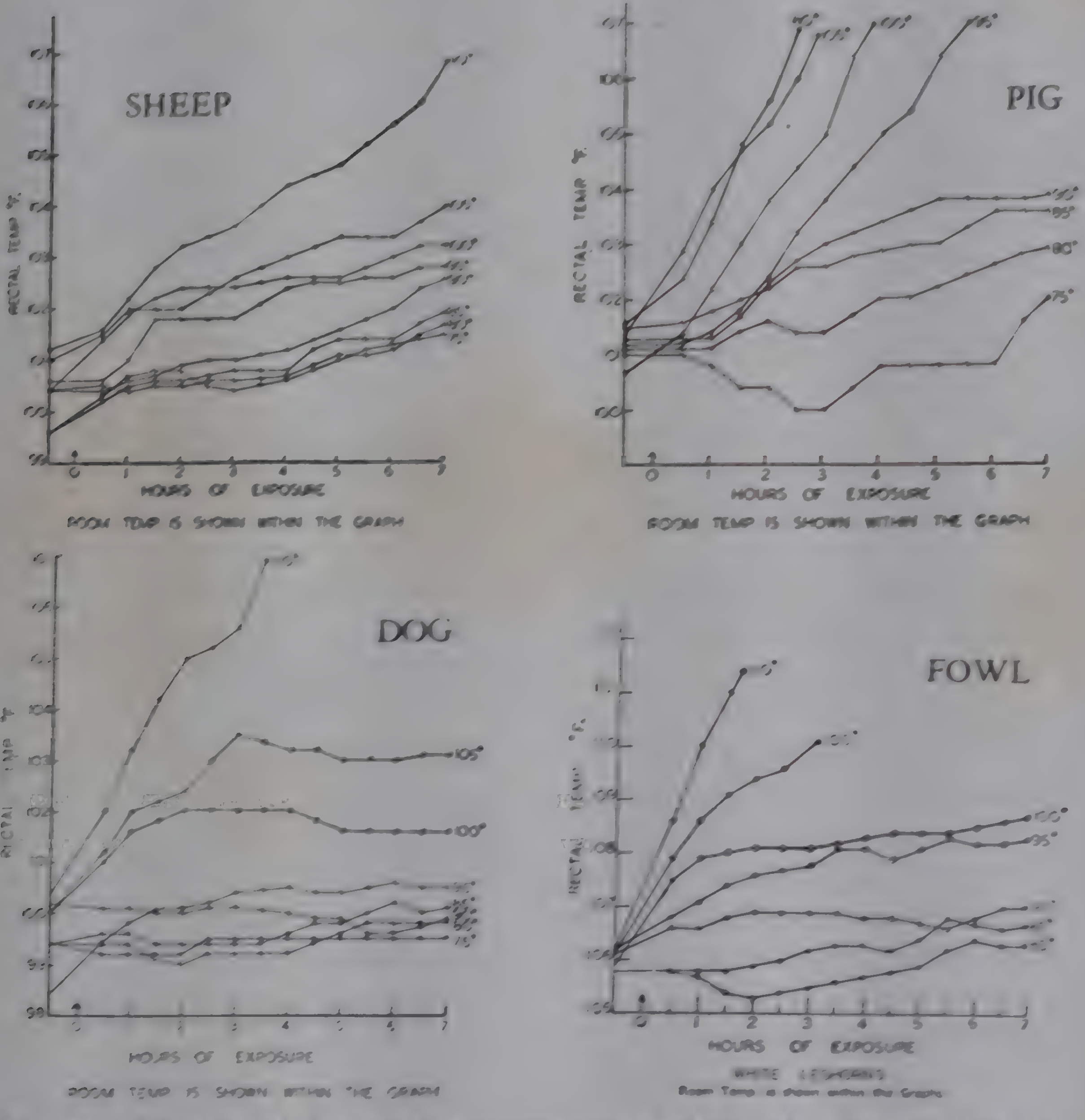


FIG. 123.—Reaction of the rectal temperatures of sheep, pig, dog, and fowl to hot atmospheres of different temperatures but of the same relative humidity (65 per cent). (From Lee and co-workers, *Proceedings of the Royal Society of Queensland*, **1941, 53**.)

atmospheric temperatures on animals will find these studies very valuable.

The rectal temperature of the *sheep* rises above normal at an air temperature of 90 degrees F. Open-mouth panting begins at a rectal temperature of 106 degrees F. A rectal temperature of 107 degrees F. is near the danger point. Unless the relative humidity is high (above 65 per cent), the sheep is able to withstand for hours an air temperature as high as 110 degrees F. The sheep appears to tolerate high environmental temperatures better than the other animals studied. This may be because of the protection against external heat which the wool affords. The sheep does not use the panting mechanism for cooling as efficiently as the dog does.

The rectal temperature of the *pig* begins to rise above normal at an environmental temperature of 85 to 90 degrees F. If the relative humidity is 65 per cent or above, the pig cannot tolerate prolonged exposure (7 hours) to an environmental temperature of 95 degrees F. At an environmental temperature of 105 degrees F., the pig is unable to stand an atmosphere of any humidity. (In these experiments the pigs had no opportunity to seek out wet places.) A rectal temperature of 107 degrees F. is near the danger point for the pig. If collapse occurs, hosing the animal with water is an effective method of resuscitation.

The rectal temperature of the *dog* tends to rise above normal at a room temperature of 80 to 85 degrees F. If the relative humidity is low, the effect of a hot environment is less severe. As the environmental temperature rises, the rate of breathing also rises but the depth of breathing (tidal volume) is markedly reduced. This helps to protect the carbon dioxide content of the blood against reduction. At a rectal temperature of 105 degrees F. the dog is in danger of a breakdown in it thermal equilibrium. At a rectal temperature of 109 degrees F., severe nervous symptoms develop with danger of immediate collapse. Sousing the animal with water leads to recovery.

The rectal temperature of the *cat* begins to be elevated at an air temperature of 90 degrees F. At a relative humidity above 65 per cent, the cat is unable to withstand prolonged exposure to an environmental temperature of 105 degrees F. Respiration rate tends to increase before the rectal temperature rises. As the rate of breathing increases, the tidal volume is only slightly reduced. Thus it would seem that the cat is less able than the dog to protect its blood carbon dioxide content against lowering, but other factors may enter into the picture for the cat. For instance, the cat augments heat loss in a hot environment by spreading saliva on the coat, and therefore is not so dependent on vaporization from the respiratory passages. In this connection it may be recalled that stimulation of the sympathetic nerves to the submaxillary gland of the cat leads to a copious flow of watery saliva, whereas in the dog similar stimulation leads to a scanty secretion of thick saliva (p. 264).

At air temperatures above 80 degrees F., the *hen* begins to show disturbances of body temperature and respiration. Prolonged exposure of a hen to an air temperature of 100 degrees F. is unsafe unless the relative humidity is below 75 per cent. A rectal temperature of 113 degrees F. for the hen is the upper limit of safety. The Leghorn hen is superior to the Australorp in heat regulation at high temperatures.

Temperature regulation in birds has been studied by Randall and Hiestand and by Randall. The relationship between body temperature and genetic resistance to infection in chicks has been investigated by Scholes and Hutt. The variability of the body temperature of the chick has been studied by Lamoreux and Hutt. There is a posthatching rise of several degrees in the temperature of the chick. This occurs during the first week, more especially during the first four days, after hatching.

The reactions of the dairy cow to increasing environmental temperatures have been studied by Regan and Richardson, and the effect of low temperatures on production and feed consumption of the cow have been investigated by Dice.

The work of Rhoad in Louisiana in determining genetic differences in the adaptability of cattle to tropical or subtropical environments should be noted. A simple test of heat tolerance has been devised. It is based upon the efficiency with which the animal disposes of heat, that is, prevents a febrile rise of body temperature, under standard conditions of exposure to a high air temperature. The body temperature taken at the end of the exposure period is the factor used in evaluating efficiency of heat disposal. Purebred and halfbred Brahman, or Zebu, cattle have been found to be more efficient in the regulation of body temperature under tropical and subtropical conditions than the European breeds. The heat tolerances of various breeds and crossbred types have been determined. The effect of atmospheric temperature on body temperature and respiration rate of Jersey cattle has been studied in Louisiana by Gaalaas (1945). A definite relationship between the temperature of the air and the body temperature of the cows, as well as the respiration rate, was noted. At an average air temperature of 50 degrees F., the average body temperature was 101.0 degrees F. and the average respiration rate 20 per minute. At an average air temperature of 95 degrees F., the average body temperature was 103.2 degrees F. and the average respiration rate 90 per minute. Further studies on Jersey cows have been made (Gaalaas, 1947).

FEVER

"Fever may be defined as any condition of positive heat balance not due solely to food, exercise, or environment" (Barbour). The experimental evidence indicates that in fever the heat-eliminating mechanism more than the heat-producing mechanism is primarily at fault. The increase in heat production that occurs in fever appears to follow van't Hoff's law, according to which the velocity of a chemical reaction increases two to three times for a temperature increase of 10 degrees C. A rise of 1 degree C. in body temperature should therefore cause an increase of 10 to 20 per cent in the basal metabolism. Actual measurements in man show an average increase of about 13 per cent for each rise in body temperature of 1 degree C. The increased metabolic rate is therefore more the result than the cause of the high temperature. The blood in fever, at least in certain forms, becomes concentrated and heat elimination at the surface of the body is inefficient. This leads to heat retention and the temperature rises. This in turn causes an increase in the metabolic rate. At some point in the elevation of body temperature, heat loss balances heat production and a new condition of thermal equilibrium is established. The "thermostat" in the hypothalamus is set at a higher level. The problem of fever is more complicated than this brief description indicates, and much remains to be learned about the condition. Several kinds of fever are recognized. A common form is due to infection. For further information, other sources should be consulted (Barbour, Du Bois).

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PART VII

Muscular Activity and the Nervous System

Chapter XXVIII

MUSCULAR ACTIVITY

THE muscles of the body are divisible into three kinds: skeletal, smooth, and cardiac.[1] Skeletal muscle is incapable of independent action; it reacts only when stimulated. Cardiac and most smooth muscles, on the contrary, display automatic or independent activity. There is a kind of smooth muscle that is activated not automatically but by motor nerves. Examples are the musculature of the blood vessels and the nictitating membrane (Bozler).

SKELETAL MUSCLE

Structure. Skeletal muscle consists of numerous individual fibers held together by connective tissue. Each fiber contains a number of nuclei and is believed therefore to represent the union of several myoblasts. The skeletal muscle fiber is composed essentially of fibrils, known as sarcostyles, surrounded by a fluid sarcoplasm. The sarcostyles, the contractile elements in the fiber, show peculiar cross-striations, the physiological significance of which is not known. That the structures responsible for the cross-striated appearance are not an all-important part of the contractile apparatus is indicated by their absence in certain kinds of muscle. The sarcolemma is a tough, semipermeable membrane surrounding the muscle fiber. The nuclei of the fiber are situated at irregular intervals just under the sarcolemma. The motor nerve fiber of a muscle fiber pierces the sarcolemma and ends just beneath it in a peculiar structure known as the motor end-plate. Muscle is endowed with a rich blood supply, the capillaries running in the spaces between the fibers but not entering the fibers. There is a remarkable constancy in the appearance of striated muscle in all vertebrates. The structural changes occurring in striated muscle during contraction are discussed in a review by Jordan.

Contraction of Muscle. Coincident with contraction, muscle displays certain mechanical, electrical, chemical, and thermal phenomena or changes. Much of our fundamental knowledge of the physiology of striated muscle has been obtained from studies on isolated frog muscles. There is good reason to believe that many of the facts so obtained apply equally well to muscle contraction in the intact animal, cold blooded and warm blooded.

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[1] The book "Muscle," *Biological Symposia*, 1941, **3**, contains numerous reviews in the field of muscle physiology and extensive citations to the literature.

Mechanical and Related Features. When a muscle is stimulated with a single electric shock (for example, induction shock, condenser discharge) of sufficient intensity (voltage), it responds with a contraction known as the simple twitch. Muscular contractions as they occur in the intact animal are seldom single twitches. Nevertheless they are undoubtedly composed of twitches which are fused together to form smooth contractions. The twitch is therefore regarded as the fundamental activity of the muscle fiber.

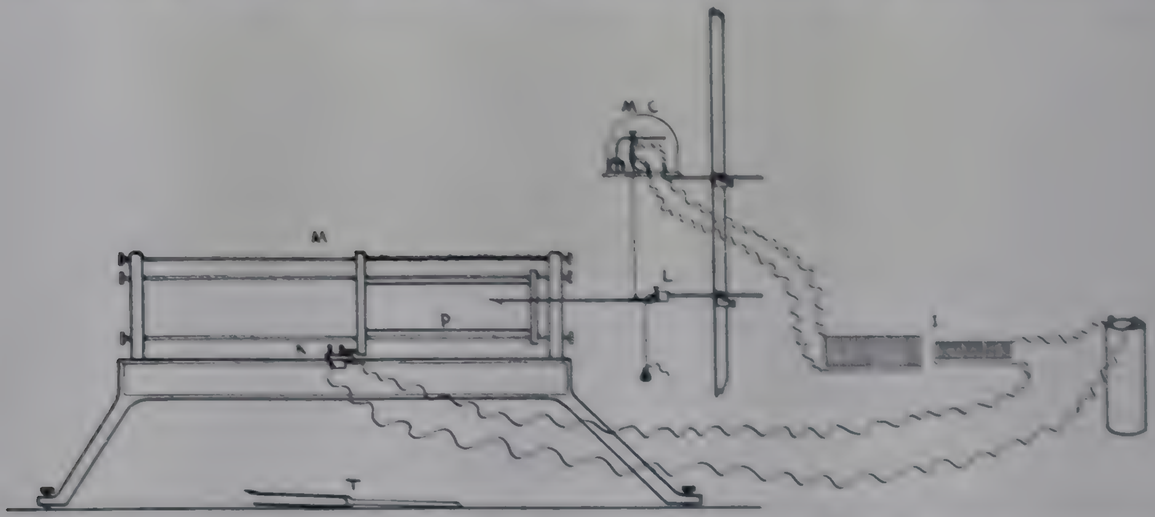

FIG. 124.—An arrangement of simple apparatus for recording isotonic contractions of skeletal muscle. The moist chamber (M.C.) contains the muscle and a pledget of cotton saturated with salt solution. This maintains a moist atmosphere and so prevents drying out of the muscle. The muscle is attached by a thread to the lever L. The spring myograph M carries a plate P, which during an experiment is covered with smoked paper and is placed in contact with the writing point of the muscle lever. The plate is then shot, by means of a spring and trigger, from one side of the myograph to the other. As it travels across, it trips the key K, which breaks the primary circuit of the inductorium I. Thereupon a current is induced in the secondary coil, and the muscle, into which the electrodes of the secondary circuit are inserted, contracts. The lever is raised and a curve traced on the paper. A time record is made with the tuning fork T. A signal magnet may be placed in the primary circuit. During the isolation of the muscle from the body, its nerve may be saved, and the muscle may be made to contract by stimulation of the nerve instead of by direct stimulation.

a. *Isotonic Contraction.* If one end of a muscle, for example, the gastrocnemius of a frog, is fixed and the other end is attached to a light lever and the muscle is stimulated, it will contract and raise the lever. A muscle contraction of this kind is said to be isotonic; the muscle actually shortens, under a constant load, and does work. In the accompanying illustration (Fig. 124) is shown an arrangement of apparatus by means of which the isotonic twitch may be recorded. The apparatus consists of a moist chamber, in which the muscle is fixed; a lever, to which one end of the muscle is attached; a myograph, for recording the contraction; and an inductorium, whose secondary coil is connected with electrodes in contact with the muscle and whose primary coil is in circuit with a dry cell. Instead of applying the electrodes directly to the muscle, they may be applied to its nerve, which is spared when the muscle is isolated from the body. Such a combination of nerve and muscle is known as a nerve-muscle preparation.

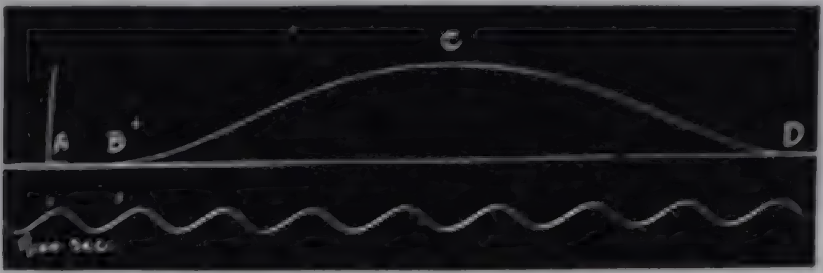

Fig. 125.—Isotonic twitch; gastrocnemius muscle of a frog. AB, latent period; BC, period of contraction; CD, period of relaxation. Although muscular contractions as they occur in the body are seldom single twitches, they are composed of twitches fused together in some manner.

A curve of the isotonic twitch, made by mechanical recording as just indicated, is shown in Fig. 125. Examination of this curve shows that it is composed of three main parts: the latent period (AB), the period of contraction (BC), and the period of relaxation (CD). The latent period is the time elapsing from the application of the stimulus to the beginning of contraction. As usually recorded in the isolated gastrocnemius muscle of the frog, it equals about 0.01 sec. When optical methods of recording are used and the muscle therefore does not have to raise a ponderous lever (isometric contraction), it is found that the latent period is much shorter than the figure just given and is less than 0.001 sec. In the intact animal, however, these very short latent periods are not found, for the muscles have to move the relatively massive bony levers of low efficiency. The duration of the period of contraction is about 0.04 sec.; the period of relaxation, 0.05 sec. or less.

Although muscle during contraction becomes shorter and thicker, it undergoes no change in *volume*. This fact has long been recognized and is not difficult to verify on the isolated muscle. The muscle is connected to electrodes and placed in a chamber filled with liquid (saline). The chamber is closed except for a capillary tube into which the saline extends. The muscle is stimulated and a twitch occurs, but the meniscus in the capillary tube does not change in position. Evidently the volume of the muscle did not change. In the intact animal, owing to the increased blood supply accompanying contraction, the muscle as a whole, but not the muscle substance itself, increases in volume during contraction.

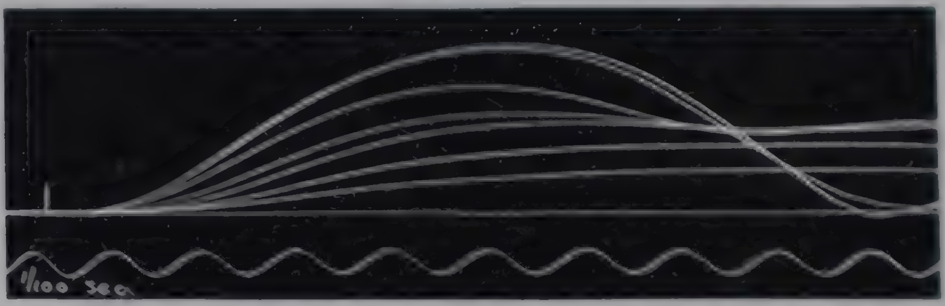

Fig. 126.—Effect of fatigue on the isotonic twitch. The muscle was stimulated repeatedly, but only every hundredth contraction was recorded. Note the lengthening of the latent and relaxation periods and the shortening of the height of contraction.

The isotonic twitch is affected by a number of factors such as fatigue, load, temperature, and drugs. The effect of *fatigue* is shown graphically in Fig. 126. As fatigue comes on, it is evident that important changes in the form of the curve take place: the latent period is increased in length, the height of contraction is lessened, and the period of relaxation is greatly prolonged. If such a fatigued muscle is allowed to rest, some recovery occurs, which indicates that the removal of fatigue products is possible, at least to some extent, in a muscle without blood supply. Accumulation of lactic acid in muscle is believed to be one of the causes of its fatigue. Doubtless other factors are concerned.

The effect of *load* is shown in Fig. 127. As load is increased, the height of the contraction is decreased and the periods of contraction and relaxation become altered in form. The amount of work done at each contraction may be calculated by multiplying the weight lifted (force) by the distance through which it was lifted. In determining distance from the tracing the magnification of the lever must be taken into account.

The changes underlying the contraction of muscle are ultimately chemical and are definitely affected by variations in *temperature*. The chemical changes apparently follow van't Hoff's law, according to which the velocity of a chemical reaction increases two to three times for a temperature increase of 10 degrees C. An increase of temperature shortens the latent and contraction periods. The gradient of the contraction is increased and the height usually decreased. The relaxation is little affected, either as to duration or gradient. A decrease of temperature has the opposite effect on the latent and contraction periods and prolongs the relaxation. There is a maximum temperature for muscle contraction beyond which irreversible changes take place in the protoplasm. For frog muscle the maximum temperature is not far from 40 degrees C.; for mammalian muscle it is a few degrees higher. There is a minimum temperature for muscle contraction, below which the muscle fails to respond to stimulation; but the loss of irritability is reversible unless the exposure to the low temperature is prolonged. The minimum temperature is near zero.

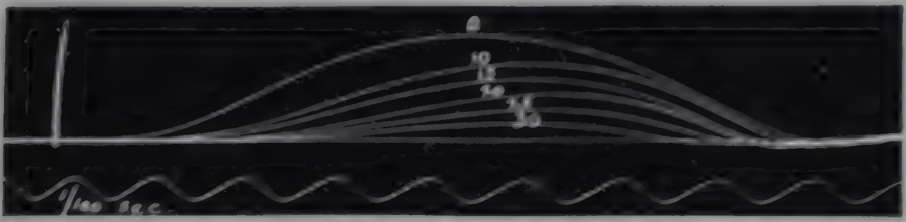

Fig. 127.—Effect of load on the isotonic twitch. The first record (0) was taken with a nonloaded lever. Thereafter weights were added to the lever as indicated by the figures (grams) on the curves.

b. *Isometric Contraction.* If a muscle when stimulated is made to pull against an immovable object, the resulting contraction is said to be isometric. The muscle develops tension but it does not shorten and therefore does no work, all the energy of its contraction appearing as heat. In efforts to determine the course of the thermal and electrical changes in muscle, studies of the isometric twitch have been of great value. If it is desired to make a graphic record of the isometric contraction, some form of isometric lever or myograph is employed and optical records are usually made. An optical isometric myograph may be made out of a stiff spring to which the muscle is attached. When the muscle contracts the spring is bent or twisted slightly, depending on the type of spring and how the muscle is attached to it, and the movement is recorded by optical projection on a photokymograph. A little mirror attached to the spring enables the movements of the latter to be projected.

A single shock applied to a muscle or its nerve will cause the muscle to make a single twitch (Fig. 125, 128). Repetitive stimuli, if their frequency is high enough, will cause the twitches to merge into smooth contractions that last for the duration of the stimulation (Fig. 129). Stimuli of intermediate frequencies will cause more or less complete fusion of the twitches, depending upon the rate of stimulation. The contraction in which there is complete fusion of twitches is referred to as *complete tetanus*, that in which there is only partial fusion as *incomplete tetanus*. In studies of the fusion of twitches, isometric optical recording gives better results than isotonic mechanical recording, for in the latter method there is the problem of the heavy lever of low natural frequency.

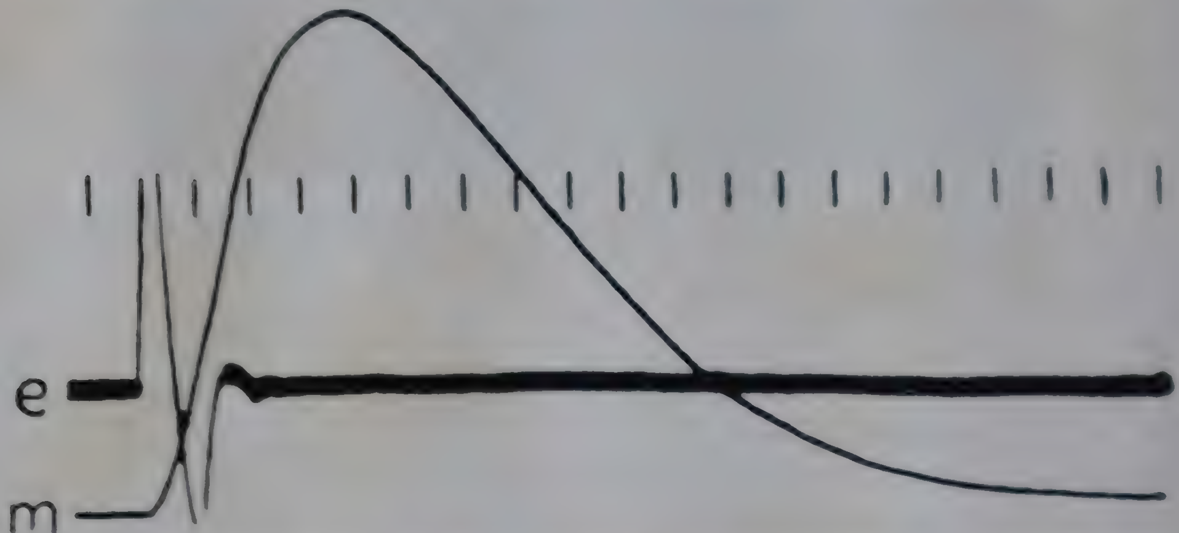

FIG. 128.—Maximal muscle twitch elicited by stimulation of popliteal nerve with a single shock: e, the electrical change; m, the isometric mechanical response. Optical recording. Note that the electrical change slightly precedes the mechanical. Time intervals, 20 msec. (From Creed, Denny-Brown, Eccles, Liddell, and Sherrington, *Reflex Activity of the Spinal Cord*, Oxford University Press, 1932.)

c. *Muscle Contractions in Intact Animals.* Isotonic contraction is characterized by tension during shortening, raising of a load, and the doing of work. Isometric contraction is characterized by tension without shortening and therefore by failure to do work. In addition, muscle may produce tension during lengthening and the lowering of a load and thus do *negative work*. The energy output here is completely degraded to heat.

In the normal animal it is evident that many of the contractions of skeletal muscle are isotonic in type. Isometric contraction can also occur, as when muscular effort is exerted against a fixed or very heavy object or when skeletal muscle is in a state of tonus (p. 617). It is equally evident that tension (contraction) during lengthening and negative work are normal features of muscular contraction. It has been pointed out by several workers that the usual division of muscle contraction into isotonic and isometric is inadequate.

d. *All-or-None Principle.* If a muscle is stimulated with a series of single shocks of increasing intensity, it is found that the contractions become greater with increases in the strength of the stimulus. There comes a time, however, when further augmentation of the stimulus causes no greater responses; the muscle is undergoing maximal contraction. The weakest contraction of which a muscle is capable is the minimal contraction, and a stimulus that evokes such a contraction is designated as a minimal stimulus. Contractions and stimuli of intervening strengths are known as submaximal. Stimuli too weak to evoke a response are said to be subminimal.

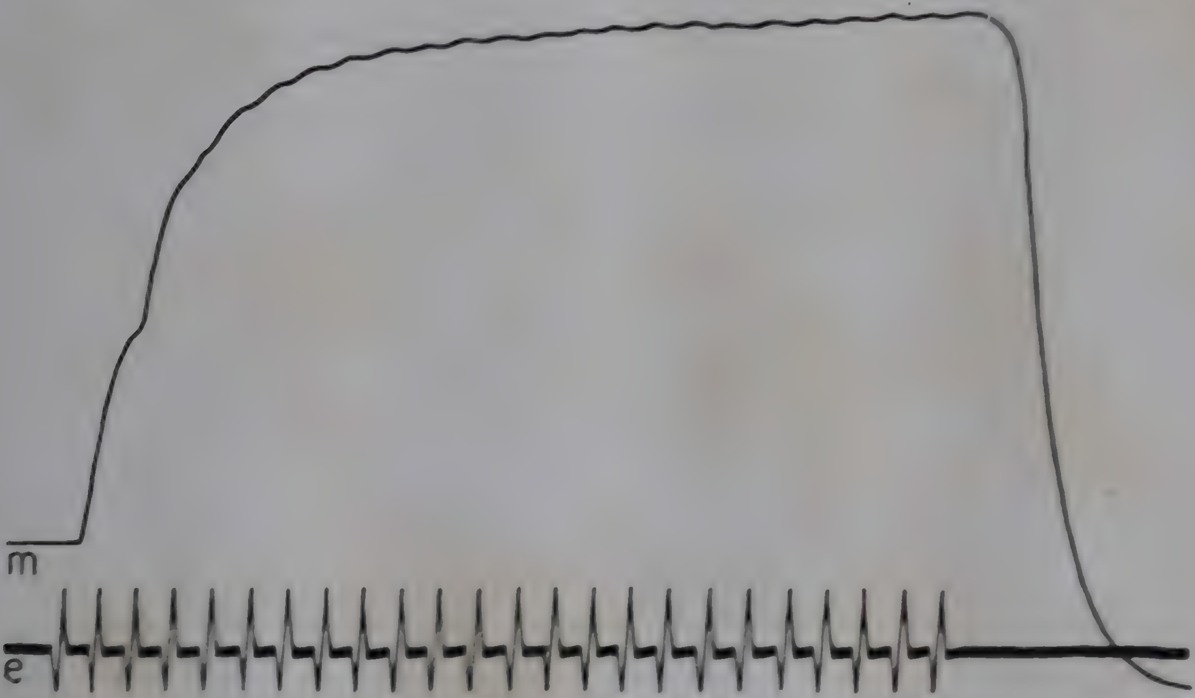

FIG. 129.—Tetanic contraction of extensor digitorum longus elicited by stimulation of its motor nerve: m, isometric mechanical responses; e, electrical changes. Optical recording. Note that fusion of the mechanical responses is nearly complete. The discreteness of the electrical responses is plainly seen. Rate of stimulation, 67 shocks per second. (From Creed, Denny-Brown, Eccles, Liddell, and Sherrington, *Reflex Activity of the Spinal Cord*, Oxford University Press, 1932.)

Cardiac muscle and also nerve have been shown to obey what is called the all-or-none principle. This means that when these tissues respond at all to a stimulus, they respond maximally. What was said above about the graded contraction of skeletal muscle to stimulation, and everyday practical experience with one's own skeletal muscles, might appear to exclude the possibility that this tissue obeys the all-or-none law. However, under the conditions of stimulation and excitation as they occur in the body, the all-or-none law applies in so far as the contraction of the individual fibers is concerned. Under certain experimental conditions not seen in the intact organism, it is possible to demonstrate a graded response of the skeletal muscle fiber.

Since under normal conditions the response of the skeletal muscle fibers is all or none, and the response of the skeletal muscle as a whole is obviously capable of gradations, it follows that some mechanism must exist which permits graded response in spite of an all-or-none response of the individual contractile elements.

e. *Innervation Ratio and Motor Unit.* Every motor nerve fiber to a skeletal muscle supplies more than one muscle fiber. This is accomplished by branching of the nerve fiber. The ratio of the number of motor nerve fibers supplying a skeletal muscle to the number of muscle fibers is known as the innervation ratio. This is for the soleus of the cat 1:120 and for the extensor longus digitorum 1:165 (Clark). There is evidence that the faster the intrinsic contraction rate of the muscle the lower is the innervation ratio, that is, the smaller is the number of muscle fibers supplied by one motor nerve fiber.

f. *Graded Response of Skeletal Muscle.* That the strength of contraction of skeletal muscles, that is, the tension they are capable of developing, may be graded in the normal animal is a familiar fact. A good deal of information is now available as to how this gradation is accomplished. The evidence is derived from studies on the isolated nerve-muscle preparation, on single motor units isolated by several delicate technics, and on intact subjects.

One way whereby graded responses are brought about is by increasing the frequency of the nerve impulses in the nerve fibers supplying the different muscle fibers by increasing the rate of firing of the neurons. With increasing frequency of nerve impulses, the muscle fibers develop increased tension. At first the active fibers may show discrete twitches, then incomplete tetanus, and, finally, if the frequency of the nerve impulses is great enough, complete tetanus. Experimental evidence indicates that those muscles which show twitches of very short duration may require several hundred stimuli per second to cause complete tetanus, whereas those that show twitches of long duration may require as few as 30 stimuli per second. Other muscles show intermediate fusion frequencies. Pale muscle is rapid, red muscle is slow. During muscle contraction in the intact animal, the maximal frequency of nerve impulses that can be attained in the motor nerve fibers is somewhat less than 100 per second. During contraction of muscle under normal conditions, the frequencies of the nerve impulses in the different nerve fibers of the motor units are not the same. The completeness of fusion of the twitches of the muscle fibers of the different units is therefore not the same and the tensions that develop likewise differ.

Another way whereby graded contraction of skeletal muscle can be brought about is by recruitment, or bringing into activity, of additional motor units. With increasing numbers of functioning motor units, the tension developed by the muscle also increases. As noted above, the frequency of impulse transmission in the nerve fibers of the different active motor units is not the same. Some are conducting at low frequencies, others at intermediate frequencies, and still others at high rates. Since the different motor units are out of phase with one another, the resulting muscle contraction is smooth, even though the muscle fibers are being stimulated at frequencies too low to cause complete fusion of their contractions.

Electrical Responses. If two points on the surface of an uninjured muscle or nerve are connected by means of electrodes to a sensitive galvanometer or other suitable electrical detector, the instrument shows no potential difference. All parts of the tissue are in the isoelectric state, that is, are at the same electrical potential. If, however, one end of the tissue is stimulated by a single shock (induction shock, condenser discharge), a *negative* electrical change passes from the stimulated end to the unstimulated. As it travels it passes first under one electrode and then the other and thus gives rise to deflections of the electrical detector. A record of the deflections may be made on a photographic surface. One thus obtains a record of the *spike potential*, or *action potential*, as the traveling electrical disturbance is called. Such a record shows two deflections, one positive and one negative, and is therefore said to be *diphasic*. The first deflection occurs when the wave of electrical change passes under the first electrode, this region now being negative to the unstimulated (positive) part of the tissue. The second deflection occurs when the wave passes under the second electrode (Fig. 130).

When an isolated muscle or nerve is injured at one end, this point becomes electrically negative to the rest of the tissue. If the injured and uninjured portions are now connected through a galvanometer, a potential difference between the two parts will be evident. This is the *injury*, or *demarcation*, *potential*. The injury acts like a stimulus in that it causes the injured part to be negative to the rest of the tissue. If the uninjured end of the tissue is now stimulated, an electrical change is set up, which, passing under the proximal electrode, will cause a momentary disappearance, or negative variation, of the injury potential. The action potential will not reach the second electrode because conduction is interrupted by the injured region. Thus a *monophasic spike potential* can be recorded.

Experiments made in an effort to correlate the electrical and mechanical responses of muscle show that the former response precedes the latter, though by a very brief interval (Fig. 128). It is also found that the electrical response is invariably followed by a mechanical response, and the opposite is probably also true—that the mechanical response cannot occur when the electrical response is absent. Since all kinds of excitable tissue show an electrical change when in action, the electrical change that accompanies muscular activity is not a peculiar property of muscle.

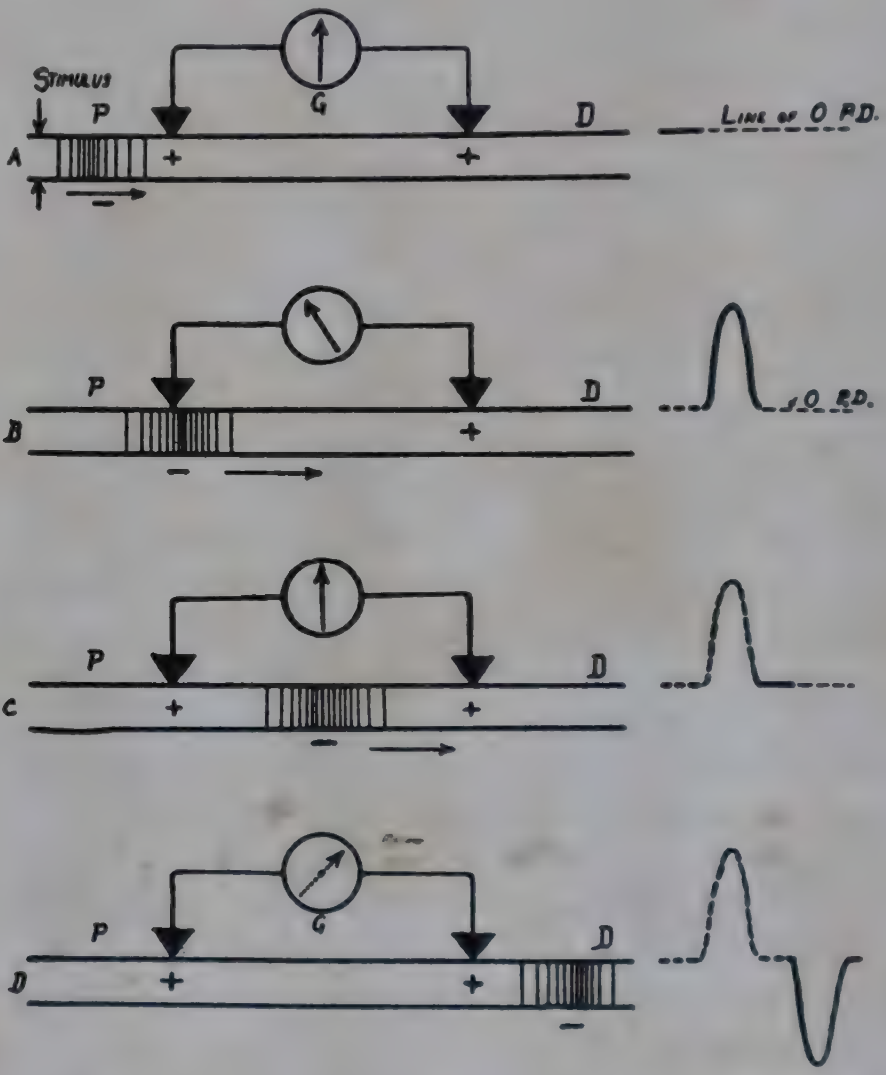

FIG. 130.—Diagrams to show the passage of a negative electrical change along a fiber (muscle or nerve).

A. The stimulus is applied, but the electrical change has not yet reached either electrode, so that zero potential is shown by the galvanometer.

B. The electrical change has reached the first electrode, and potential difference is shown.

C. The electrical change is between the electrodes, and zero potential is again evident.

D. The electrical change has just passed the second electrode, and the potential is returning to zero.

The diagrams at the right represent the photographic record of the movements of the galvanometer string. The record is diphasic. (From Fulton's *Muscular Contraction and the Reflex Control of Movement*, The Williams and Wilkins Company, 1926.)

Chronaxie. The excitability of different tissues varying a great deal, it is desirable to have some common basis for the comparison of excitabilities. One way in which comparison may be made is by a determination of the latent period. Another way is by finding the threshold (minimum) strength of stimulus necessary to excite in an indefinite time. Still another way to express the excitability of a tissue quantitatively is in terms of *duration* of effective stimulus. Such a measure of irritability is known as the chronaxie, which may be defined as the shortest duration of twice the threshold, or rheobasic, strength of current necessary to excite. The chronaxie of certain muscles is as follows: frog's gastrocnemius 0.3 msec., frog's rectus abdominis 0.9 msec., frog's ventricle 3.5 msec., frog's stomach 30 to 100 msec. In general, the more excitable tissues have a shorter chronaxie. The subject of chronaxie, together with the newer developments, has been critically reviewed by Davis and Forbes.

Chemical Changes and Energy Exchanges. The chemical changes and energy exchanges of skeletal muscle have been extensively studied in recent years. In these researches use has been made of isolated skeletal muscles of frogs, of mammalian muscles having an adequate blood supply, and of the enzyme systems present in muscle extracts.

The generally held view regarding contraction and relaxation of muscle is that these processes take place without the aid of oxygen; they are entirely anaerobic. Oxidation occurs only during the recovery phase. Muscle is therefore an anaerobic mechanism. Only recovery is oxidative. According to this view, muscle is often called upon to release energy more quickly than could be supplied by direct oxidation. The survival value of an explosive release of a large amount of energy, not dependent upon oxidation, and the quick muscular contraction resulting therefrom is obvious. Muscle has been compared to a storage battery which is able to discharge quickly a large amount of energy not derived directly from oxidation but stored by means dependent upon oxidation (running engine). The spring analogy is sometimes used. Muscle is like a wound-up spring. Trip the catch and a large release of energy occurs, but the spring has to be wound up again by some force ultimately dependent upon oxidation.

Following is a summary of the main chemical changes and energy exchanges associated with anaerobic contraction: (1) Adenosine triphosphate (ATP), a nucleotide occurring in muscle, breaks down into phosphoric acid and adenylic acid. This reaction supplies the energy for contraction as well as phosphoric acid for the phosphorylation of glycogen (p. 485). (2) Phosphocreatine (phosphagen, creatinephosphoric acid) is hydrolyzed to creatine and phosphoric acid. This reaction furnishes energy that is used to resynthesize ATP from adenylic acid and the phosphoric acid derived from phosphocreatine. Relaxation occurs. (3) During contraction and relaxation, and for some time thereafter, pyruvic acid (or, if the oxygen supply is inadequate, lactic acid) is formed from glycogen by a series of reactions shown on pp. 236 and 487. The energy derived from these reactions is used to resynthesize phosphocreatine from creatine and the phosphoric acid released by the conversion of phosphorylated glycogen to pyruvic acid (glycolysis). (4) Pyruvic acid is oxidized to carbon dioxide and water (p. 488). This reaction contributes energy to the resynthesis of ATP from adenylic acid and phosphate. This is where energy derived from oxidation comes into the energy-production system of muscle.

It is evident from this summary that the immediate source of the energy for muscle contraction is ATP. The hydrolysis of this compound, as well as of phosphocreatine, releases a large amount of energy, which in the first instance is used for muscle contraction and in the second for the resynthesis of ATP. The energy stores of these organic compounds are associated with phosphate linkages, and this potential energy has been designated as phosphate-bond energy. The compounds themselves are spoken of as power phosphates (p. 237). The energy released by glycolysis goes back into the power phosphates. The pyruvic acid formed in the glycolytic process is oxidized to carbon dioxide and water, and energy resulting from this oxidation likewise goes into the energy-rich phosphate compounds. Oxidation not only yields energy but it prevents the accumulation of pyruvic acid (or lactic acid) in the muscle. A considerable decrease in intracellular *p*H would prevent the functioning of the enzyme systems which are now known to catalyze the chemical reactions that bring about the energy exchanges of muscle. If the *p*H of the cells changes unduly, the catalyzers fail to function properly. One of the factors in fatigue is the accumulation of lactic acid in muscle.

It is an old question as to how chemical energy is converted into mechanical energy in muscle contraction. No definite answer is available, but recent evidence suggests that the energy released by the hydrolysis of ATP is absorbed by the myosin molecules of the muscle fibers: these molecules are arranged in linear series and contract simultaneously when they accept the energy released by ATP. In this way myosin may act "as a kind of transformer element for the conversion of chemical energy to mechanical energy" (Green).

Carbohydrate is the preferential *fuel of muscle*. There is no doubt, however, that fatty acids can be oxidized by the muscle and other cells, probably after conversion to acetic acid and the ketone bodies (p. 480).

Although energy transformations have been studied more fully in skeletal muscle than elsewhere in the organism, there is increasing evidence that the same basic mechanisms are employed in secretion, absorption, and other energy exchanges. So far as brain is concerned, carbohydrate is the exclusive fuel, and most of the energy of brain is derived aerobically.

In connection with the foregoing summary, the discussions on physiological oxidations, especially on glycolysis, and the pertinent parts of the chapter on carbohydrate metabolism should be studied (pp. 233 and 486). For further details other sources should be consulted.

Oxygen Debt. Anaerobic contraction allows muscle to develop an *oxygen debt*, which under conditions of intense activity may be very great. Thus, according to Brody, horses and men may, during very intense muscular work, expend energy at 100 times the resting rate. Such activity cannot be long maintained because of the onset of fatigue. After such an output of energy, the oxygen debt must be paid by the oxidative removal of lactic acid. An expenditure of energy eight times as great as during rest may be shown during prolonged hard work. Under these condtions oxidation keeps pace with energy expenditure. It is presumed, however, that the energy release follows the anaerobic pathways indicated above.

Aerobic Contraction. In recent years evidence has been presented by Sacks and other investigators that anaerobic release of energy in muscle occurs only during conditions of inadequate oxygen supply, as in the early stages of muscle contraction when an increased blood flow through the muscle is not fully established, and during severe muscular effort. At other times the energy is derived directly from oxidative chemical reactions not involving phosphate-bond energy. To what extent these ideas, emerging largely from experiments in which an adequate blood supply was maintained to the muscle under study, will prevail against the classical theory of energy release cannot be stated at present.

Thermal Changes. It is a familiar fact that muscular contraction is accompanied by increased heat production. The thermal changes occurring in muscle have been measured by the use of thermopiles and highly sensitive galvanometers. The muscle is so arranged that when stimulated it will contract isometrically. Under these conditions all the energy liberated appears as heat. Thus the energy that is ordinarily realizable as external work is transformed into heat. When the muscle is stimulated so as to give a brief isometric contraction, it is found that the evolution of heat is in five phases. The first three are designated as the *initial heat*. The last two are known as the *recovery heat*. The first outburst of heat occurs at the onset of contraction, the second during the maintenance of contraction (this heat is absent in the simple twitch), the third during relaxation, and the fourth and fifth during recovery.

The heat of the first two phases—the *contraction heat*—is associated with the breakdown of ATP and phosphocreatine and cannot be used for work. In this sense it is wasted. The *relaxation heat* is the result of the degradation of tension into heat and represents the maximal amount of energy that could be converted into work if the muscle were contracting isotonically. It may be as great as 35 per cent of the total initial heat. The amount of the initial heat is the same whether the muscle is contracting in the absence of oxygen or in the presence of it.

The recovery heat in the absence of oxygen is designated as the *delayed anaerobic heat*. It is believed to represent the energy that is lost as heat when pyruvic acid (or lactic acid) is produced. It cannot be returned to the power phosphates and therefore cannot be utilized for work. It is wasted so far as the performance of work is concerned. In the presence of oxygen the recovery heat is augmented by the *oxidative heat*. This represents the energy that is degraded to heat when pyruvic acid is oxidized; the rest of the energy goes to the resynthesis of ATP.

The thermal changes occurring in muscle contraction may be summarized as follows:

- Initial heat
  - **Contraction heat**
    - **At onset of contraction (1)**
    - **During maintenance of contraction (2)**
  - **Relaxation heat (3)**
- **Recovery heat**
  - **Delayed anaerobic heat (4)**
  - **Oxidative heat (5)**

Rigor Mortis. When skeletal muscle dies, that is, when its characteristic reactions become irreversible, it gradually shortens and the animal stiffens. The muscle is said to be in a state of rigor mortis. The rate of development of rigor mortis is influenced by the antemortem condition of the animal and other factors. If the animal was fatigued, it develops quicker. Heat hastens and cold delays its appearance. In rigor profound changes take place in the muscle proteins but the exact nature of the changes is not known. It was formerly thought that lactic acid formation and the resulting decrease in muscle *p*H were the essential factors responsible for the changes in the muscle proteins, but this view is not now held. Ordinarily rigor disappears in 10 to 12 hours after its onset, but it may last for a much longer time.

SMOOTH MUSCLE

Smooth muscle is widely distributed in the body, being found in the walls of hollow organs or structures such as stomach, intestine, bladder, uterus, artery, vein, gland duct, and respiratory passage, and in other locations. According to Bozler there are two principal kinds of smooth muscle. One kind is composed of many units, is activated by true motor nerves, and in these respects is comparable to skeletal muscle. The musculature of the blood vessels is an example. The other is syncytial, shows an automatic rhythm, and in these respects resembles cardiac muscle. The smooth muscle of the gastro-intestinal tract is an example.

Tonus. Most smooth muscle possesses a varying degree of tonus, which may be defined as its resistance to extension. Tonus of smooth muscle is accompanied by only slight expenditure of energy, and the increased production of lactic acid in tonus is slight. There is, however, probably no fundamental difference between tonus of smooth muscle and contraction (Evans, 1926; Fischer).

Rhythmicity. Most smooth muscle possesses the power of spontaneous or automatic contraction. Thus a bit of intestine suspended in warm, oxygenated Locke's solution may beat for hours. The balance of evidence at present indicates that the spontaneous contraction of gastro-intestinal muscle is myogenic rather than neurogenic in origin. Other smooth muscle possessing an automatic rhythm is probably like gastro-intestinal muscle in this respect.

Contraction. When smooth muscle is made to contract in response to a single stimulus, it is seen that the contraction is much slower than in skeletal muscle; the latent, contraction, and relaxation periods are all longer.

Lactic acid is formed in smooth muscle under conditions similar to those that cause its formation in skeletal muscle. A definite rigor seems not to occur when smooth muscle dies or is killed by heat, chloroform, or injury.

Chapter XXIX

THE ACTIVITY OF PERIPHERAL NERVE

NERVOUS tissue consists of neurons, which are supported by a special type of connective tissue termed neuroglia. A neuron, the genetic, structural, and functional basis of the nervous system, is a nerve cell. It consists of a cell body and all its processes, which are usually of two kinds: dendrites and axon. (Some neurons lack dendrites.) According to another, though less correct, usage the term nerve cell comprises the cell body, the dendrites, and only the proximal part of the axon. Nerve cell bodies are limited in location to the gray matter of the brain and spinal cord and to the spinal, cranial, and autonomic ganglia.

Dendrites are the short processes of a nerve cell. The number arising from a single cell may vary from one to many. Their function is to conduct nerve impulses to the cell body. Their structure is similar to that of the cell body. They terminate at no great distance from the cell body from which they spring and therefore do not enter into the formation of nerve fibers.

NERVE FIBERS

A nerve fiber comprises the axon and its coverings. According to a common usage, the nerve fiber is regarded as commencing at the point of emergence of the axon from the gray matter of the central nervous system or from a ganglion. That portion of the axon which is continued into the nerve fiber is sometimes designated the axis cylinder. Since an axon runs an unbroken course from its parent cell body to its place of termination, it is evident that its length may be very great. Axons terminating in the foot, for example, have their cells of origin in the gray matter of the lower part of the spinal cord. The axon, whose structure is not well understood, is usually described as consisting of fibrils imbedded in axoplasm. Although the actual existence of these fibrils in the living state is questioned by some workers, recent evidence supports the old view that they are normal structures, that is, not artifacts.

Most axons possess coverings or sheaths. These are of two kinds, the myelin, or medullary, sheath and the neurilemma. The myelin sheath is a whitish cylindrical covering varying in thickness in different nerve fibers. At intervals in the course of the nerve fiber, this sheath is completely interrupted by circular constrictions known as the nodes of Ranvier. Myelin is of homogenous structure and is nonnucleated. It contains a large amount of lipids, the principal ones being cephalin, lecithin, cholesterol, and cerebrosides. The neurilemma is a thin, delicate covering found outside of the myelin sheath. At the nodes of Ranvier it touches the axon. Most of the fibers of the cranial and spinal nerves are myelinated and possess a neurilemma. Generally speaking, postganglionic sympathetic fibers are nonmyelinated but show the presence of the neurilemma.

Peripheral nerve fibers are united into masses known as nerves or nerve trunks.

Afferent and Efferent Nerve Fibers. According to the direction in which they conduct nerve impulses, peripheral nerve fibers are divided into two classes, afferent and efferent. Afferent nerve fibers conduct impulses from a receptor (sense organ) to the central nervous system. The cells of origin of such fibers are located in the dorsal root ganglia of the spinal nerves and the corresponding ganglia of the cranial nerves. Afferent nerve fibers conduct impulses in the opposite direction, that is, from the central nervous system to the effector—muscle or gland. Their cells of origin are located in the gray matter of the central nervous system or in the ganglia of the autonomic nervous system.

THE NERVE IMPULSE

When a nerve fiber is stimulated at or above threshold intensity, it manifests the phenomenon of excitation which is followed by the propagation or transmission of a physicochemical change known as the nerve impulse. The nerve impulse is self-propagated. This means that the energy for transmission comes from the fiber over which the impulse travels.

In experiments on the excitation of nerve, muscle, and other forms of protoplasm, the electrical stimulus is commonly used. It may be in the form of induction shocks, condenser discharges, sinusoidal alternating current, or direct current.

Experimentally a nerve may be stimulated anywhere in its course, whereupon a nerve impulse travels in both directions along the fiber. Under normal conditions, however, there is no provision for such stimulation: a nerve impulse is generated only at one end of the nerve fiber. In the case of afferent fibers such stimulation is effected through the intermediation of the receptor, whereas in the case of efferent nerve fibers the stimulus arises in the cell body, usually as the result of the action of impulses from another neuron.

When a nerve is adequately stimulated either experimentally or under normal conditions, a nerve impulse arises. In a single fiber this consists of a single impulse or, if the stimulus is more intense, a train of impulses. When the entire nerve is stimulated by a single shock of suitable intensity, a single volley of impulses is transmitted and if the stimulus is either repetitive or of greater intensity a series of volleys will result. The frequency of the nerve impulses is usually between 200 and 400 per second when the nerve fiber is stimulated directly, between 25 and 60 when a receptor is stimulated, and between 10 and 90 when the motor nerve fiber is conducting (Adrian, 1930).

The nerve impulse is believed to be qualitatively the same under all conditions and in all kinds of fibers, afferent and efferent, the only differences being in the frequency of the impulses, the velocity, and the magnitude. The *frequency* of the impulses increases with the intensity of stimulation. The *velocity* is constant from time to time in a given fiber if the conditions are the same. However, variations in velocity are met with in different fibers because of differences in their cross-sectional area. The larger the fiber the greater is the velocity of conduction in it. In mammalian nerve, the velocity of the nerve impulse, in the different fibers, ranges from approximately 0.5 to 100 meters a second. The velocity of nerve impulses and their frequency should not be confused. A comparison of nerve impulses to a stream of bullets issuing from a machine gun may not be inappropriate. The stream of bullets corresponds to a train if impulses in a nerve fiber. The velocity of the bullets is always the same, but the frequency with which they are discharged from the gun can be varied. The *magnitude* of the nerve impulse in a given fiber (as measured by the voltage of the spike potential) is also constant under normal conditions. As between different fibers, however, variations in magnitude of the impulse are seen. These differences, like velocity of transmission, are directly related to fiber size. Their significance is not well understood.

Decrementless Conduction and All-or-None Character. That the nerve impulse is some form of energy transmission, however slight, is clearly indicated by the fact that the effector (muscle, gland) is thrown into activity by the nerve impulse, that is, receives energy from the nerve impulse. In trying to reach some conclusion concerning the nature of the energy that constitutes the nerve impulse, one of the first questions to be considered is whether the impulse travels along the nerve fibers in a passive manner much as sound waves travel in a tube, or whether the nerve fiber contributes actively to the passage, like the propagation of combustion along a fuse. In the first case the nerve impulse would progressively diminish as it traveled, whereas in the second case it would suffer no decrement but might, under suitable circumstances, even show an increase. In an effort to answer these questions physiologists have devised experiments in which nerve impulses are made to encounter regions of decreased conductivity brought about by the application of an anesthetic or heat or cold to the nerve. It has been found that when the impulse emerges from the region of decreased conductivity it quickly flares up to its normal level. This shows that the nerve impulse is not a passive phenomenon, and must be regarded as an active propagation somewhat analogous to the passage of combustion along a fuse. The nerve fiber therefore contributes actively to the passage of the impulse and is not a passive conductor.

The fact that the nerve impulse upon emerging from a region of decrement resumes its former intensity signifies that it obeys the all-or-none law. Otherwise it would not return to its former level as soon as conditions became favorable. Other evidence indicates that the all-or-none law is valid for nerve, that is, that the response of nerve is always maximal regardless of variations in the strength of stimulus above the threshold. In other words, the nervous system cannot change the magnitude of the nerve impulse; nor can it alter the quality. The frequency of the nerve impulses is apparently the only variable that a given nerve fiber can conduct. The frequency depends on the intensity of stimulation.

It may therefore be stated as a fundamental principle in nerve physiology that the nerve impulse is an actively propagated disturbance, that it is normally conducted without decrement, and that it obeys the all-or-none law.

Changes Accompanying the Passage of the Nerve Impulse. The nerve impulse being an active propagation and not a passive wave, it follows that changes of some kind must take place in the nerve fiber as the impulse travels along. Until recent years the only accompaniment of the nerve impulse that was definitely proved to exist was the electrical change known as the action potential. More recently other changes in nerve have been shown to occur. These include heat production, oxygen consumption, and carbon dioxide and ammonia production.

Refractory Period. Nerve, like muscle, shows a refractory period, by which is meant that following the passage of a nerve impulse there is a short interval during which the nerve is incapable of being excited. Stimulation during this time is quite ineffective. The duration of this *absolutely refractory period* varies from 0.4 to 2 msec. in the different fibers. Following the absolutely refractory period there is a *relatively refractory period,* about 10 msec. in duration, in which excitability is returning. Under some conditions this period of returning excitability may be followed by one of supernormal excitability. If the nerve impulse was merely a passive phenomenon, nerve would hardly show a period during which it could not be stimulated. The fact that nerve does show a refractory period is taken as further evidence that the passage of the impulse is an active phenomenon which results in some change in the nerve fiber that is repaired during the refractory period. A refractory period signifies discontinuous action and indicates obedience to the all-or-none law.

The duration of the refractory period places an upper limit on the number of impulses that a nerve fiber can conduct in a given time. Under experimental conditions frequencies higher than 1000 per second have been recorded in some mammalian nerve fibers, and a frequency of 400 impulses per second has been observed in nerves under normal conditions of stimulation. However, it seems likely that most nerves normally conduct at frequencies not greater than 100 per second.

Electrical Change. Many kinds of protoplasm, probably all kinds, show an electrical change during activity. (See also pp. 88 and 561.) That active nerve displays such a change, known as the action potential, or spike potential, has long been recognized. It is an invariable accompaniment of the nerve impulse, and in nerve physiology the detection of an action potential is regarded as proof that a nerve impulse is passing. It is the manifestation of the passage of the nerve impulse that is most readily detected. The action potential may be detected and recorded by the use of several kinds of instruments, namely, the string galvanometer, the capillary electrometer, or the oscillograph, of which there are various types.

By means of the cathode ray oscillograph—a mechanism which, unlike the galvanometer, draws no current and has no inertia—it has been shown that the action potential is more complicated than the evidence from the use of the string galvanometer reveals. The explanation of this difference in the records obtained with the two kinds of detectors lies in the fact that the string galvanometer gives a composite picture of the potentials in all the nerve fibers of the stimulated nerve trunk, whereas the more complicated picture presented by the cathode ray oscillograph is due to its ability partially to separate the potentials of different nerve fibers or groups of fibers. The main difference between the spike potentials of different fibers is in their velocity, which appears to vary directly as the diameter of the nerve fiber. Depending on the velocity of their spike potentials, different nerve fibers can be placed in several groups, and it has been shown that the different groups have anatomical and physiological significance. Three major elevations in the electrical records as made by the electron oscillograph are recognized (Fig. 131). The A elevations represent fibers with velocities ranging between 100 and 20 meters per second. They are the somatic myelinated fibers. The B and C elevations represent fibers with much lower velocities. The B fibers are autonomic myelinated fibers. The C fibers are nonmyelinated. The velocities of fibers in the dorsal roots of the spinal nerves range from 100 to 0.5 meters per second; in the motor nerves supplying skeletal muscle, 100 to perhaps as low as 2 meters per second; in the sympathetic outflow, 2 to 0.5; and in afferent fibers related to the sympathetic system, 10 to 0.5. These topics are fully elaborated in a monograph by Erlanger and Gasser, to which reference may be made for further information and the literature.

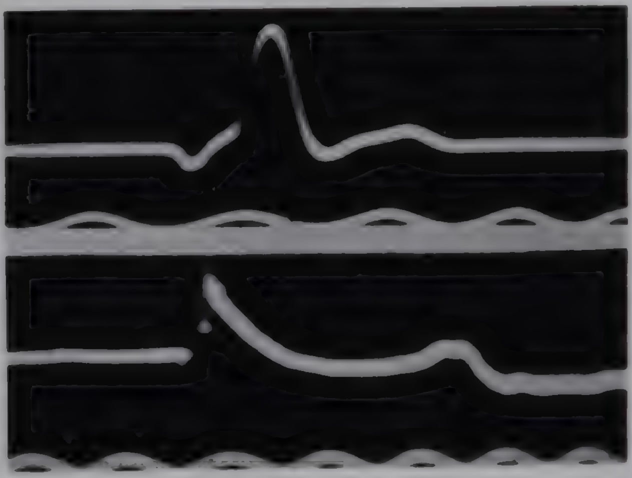

FIG. 131.—Oscillograph records of the action potential (spike potential) of mammalian nerve. The upper record is taken from the sciatic nerve of the cat and shows the faster components. The first break in the line is produced by the stimulating shock and the interval between the break and the large elevation is the conduction time. Conduction distance, 38 mm.; time at bottom of record, 0.001 sec. The velocities represented range between 100 and 20 meters per second.

The lower record, taken at much higher amplification than the upper one, shows the potentials of fibers with velocities of 1.3 meters per second and slower. Time, 0.01 sec.; conduction distance, 30 mm. The first elevation in the figure is made up of the components shown in the upper record. The three elevations—the two in the upper record and the third in the lower—are known, respectively, as A, B, and C. (Courtesy of Dr. H. S. Gasser.)

Following the spike potential there are positive and negative afterpotentials, which are of much lower voltage but of much longer duration than the spike. As to duration, the spike potential of A fibers lasts 0.4 to 0.5 msec.; the negative after-potential, 12 to 20 msec.; and the positive after-potential, 40 to 60 msec. (Grundfest). The full significance of the after-potentials is not understood, but they are known to be related to the recovery of nerve after stimulation. They are characterized by less stability than the spike potential.

Heat Production. For years investigators were unable to detect heat production in nerve during its activity. However, using improved methods, Downing, Gerard, and Hill were able to show, in 1926, that nerve during stimulation produces a small amount of heat. In the method use was made of a thermopile of great sensitivity and a galvanometer with vacuum-tube amplification. In this way it was possible to show that heat is liberated by the nerve in two phases: about 10 per cent during the stimulus and about 90 per cent following the stimulus. The heat liberated during the initial phase was, on the average, about 7.6×10^{-6} cal. per gram of nerve per second of stimulation. The total heat liberated averaged about 6.9×10^{-5} cal. per gram of nerve per second of stimulation. The duration of the prolonged phase of heat production was 9 to 11 minutes. The heat production of nerve has been further studied by Gerard, Hill, and Zotterman. These workers calculate that in frog's nerve the initial heat of a *single impulse* is about 10^{-7} cal. per gram of nerve, and the total heat about 10^{-6} cal. per gram.

The claim was made that the heat production observed in nerve under conditions such as those just mentioned is a direct result of the stimulating current and not a manifestation of normal activity accompanying the propagation of the nerve impulse. Hill reinvestigated the question with this objection in mind and reached the conclusion that heat production, like the potential change, is a normal property of the transmitted nerve impulse.

An analogy exists between muscle and nerve as regards their production of heat during activity, but the analogy is not so perfect as might be expected. Apparently the course of the metabolism in the two tissues is not identical.

Resting nerve produces a small amount of heat. The figures given above do not include the heat production of the resting metabolism but only the heat increment accompanying activity.

Oxygen Consumption. It has long been known that a nerve stimulated in the absence of oxygen loses more quickly its ability to conduct than one stimulated in the presence of oxygen. Evidently oxygen is in some way concerned in the conduction of the nerve impulse or in recovery following conduction. The modern conception is that it is used to oxidize some foodstuff, probably carbohydrate. Several workers have attempted, with considerable success, a determination of the amount of the oxygen consumption of nerve (Fenn, Gerard). Quantitative studies indicate that there is a resting utilization, which is increased during stimulation. These facts regarding oxygen consumption by nerve are additional evidence that the metabolism of nerve is comparable to that of other tissues.

Carbon Dioxide Production. The utilization of oxygen by nerve implies the production of carbon dioxide. Several investigators, using highly refined methods, have been able to show and measure the carbon dioxide production. Parker found that the quiescent sciatic nerve of the frog produces, on the average, 0.00876 mg. of carbon dioxide per gram of nerve per minute, and that when stimulated the increase of carbon dioxide elimination is about 14 per cent. When these results were corrected for the metabolism of the connective tissue of nerve, the figure for the carbon dioxide production per gram of nerve per minute became 0.008 mg. and the increase upon stimulation became about 16 per cent. Similar results have been obtained for the lateral-line nerve of the dogfish.

The respiratory quotient of nerve, as determined by Fenn, is usually between 0.9 and 1.0. Such figures as these indicate essentially a carbohydrate metabolism. Others have obtained lower values, especially in resting nerve. The respiratory quotient of brain is unity. This indicates carbohydrate metabolism.

Ammonia Production. Another metabolite that has been shown to be produced by nerve in ammonia. Tashiro, using a method by which it was possible to measure as little as 10^{-7} gm. of ammonia, showed that resting nerve produces ammonia, and that the production is increased by stimulation. The significance of ammonia production by nerve is not yet known. Adenosine triphosphate has been suggested as a source. This substance is of importance in muscular contraction under anaerobic conditions (p. 563).

The Nature of the Nerve Impulse. Just how transmission of the nerve impulse is accomplished has been the subject of much discussion and investigation. However, no fully acceptable theory is available. About 50 years ago the membrane hypothesis was proposed and it is at present the most commonly accepted idea regarding the mechanism of conduction. According to this theory, conduction occurs at the surface of the nerve fiber (or other protoplasmic mass showing the property of conduction). The neuron membrane is the seat of a potential difference with positive charges on the outside of the cell and negative charges on the inside. This condenserlike membrane is leaky and is maintained in a charged condition by the resting metabolism of the nerve. Stimulation results in a breakdown of the membrane at a point and depolarization of the membrane occurs. The adjacent normal part of the membrane now shows a potential relative to the negative stimulated part. This potential difference leads to the development of a local current which causes the depolarization of the adjacent parts of the fiber. The newly depolarized area then becomes negative to the next part, a local current flows, and the process is repeated with the result that a wave of membrane breakdown and depolarization sweeps along the nerve fiber as the nerve impulse. Immediately following the passage of the nerve impulse there is a refractory period during which the nerve repairs itself and becomes repolarized. This may occur in as brief an interval as 0.4 msec. in certain fibers. Repolarization requires energy, which accounts for the increased metabolic activity of the nerve accompanying, or, better, immediately following, the passage of the nerve impulse. Energy is thus stored up in the charged membrane, which is ready to conduct a nerve impulse when it is depolarized by a stimulus. The resting membrane is leaky and to maintain it in a polarized state energy must be expended. This accounts for the slight but constantly occurring metabolic activity of resting nerve. The energy required for repolarization of the membrane and the maintenance of the polarized state in resting nerve is doubtless derived in the long run from oxidation, but our knowledge of the exact processes involved is meager. Energy-rich phosphate compounds maintained by the oxidation of pyruvic acid may be factors.

Fatigue. From the foregoing statements regarding the nature of the nerve impulse and the metabolic changes in nerve accompanying its passage, it might be supposed that the nerve fiber—the conducting element—would, under appropriate circumstances, show fatigue. Numerous experiments indicate, on the contrary, that nerves are practically incapable of fatigue. When stimulated continuously for hours they are still capable of conducting a nerve impulse. This can be interpreted to mean that the changes accompanying the passage of the nerve impulse are quantitatively slight or are readily recovered from, or both.

It is well known that the reflex arc is capable of fatigue. Therefore, since the nerve fiber is practically nonfatigable, some other part or parts of the nerve mechanism must be involved. Certain lines of evidence make it probable that the synapse (region of contact between neurons) is the most vulnerable point (Chapter XXX). However, the cell body is probably not exempt from fatigue.

Chapter XXX

NEURONS, RECEPTORS, SENSATIONS, EFFECTORS

ALL protoplasm possesses the properties of irritability, conductivity, and correlation. In higher animals these properties are exhibited in greatest degree by nervous tissue. The nervous system, embracing the whole of the nervous tissue of the body, may be conveniently divided into the central nervous system and the peripheral nervous system. The former comprises the brain and spinal cord. The latter comprehends all other nervous tissue: the cranial and spinal nerves, their ganglia and end-organs, and the autonomic nervous system (Fig. 132). The central nervous system consists of afferent fibers (derived from the primary afferent neurons), which transmit impulses from the periphery; motor neurons, which transmit impulses to the periphery; and interneurons, which establish complex connections between afferent neurons and the motor neurons.

In its broad aspects the function of the nervous system is to enable the organism to adjust itself or its parts to changes in the external or internal environment.

THE NEURON

The nervous system is composed of nerve cells termed neurons and a supporting neuroglia. The neuron is the embryological, anatomical, and physiological unit of the nervous system. It consists of the cell body and all its processes: dendrites and axon. The term nerve cell is properly used synonymously with the word neuron, although according to another usage the nerve cell is regarded as comprising the cell body, the dendrites, and only the proximal part of the axon.

Kinds of Neurons. Although neurons present a great number of forms, it is in general possible to divide them into a few groups based on the number and arrangement of their processes. Many atypical forms occur that are difficult or impossible to classify. Following are the general classes.

Unipolar cells, those having a single process, are rarely encountered in higher animals. They are somewhat more frequently seen in lower vertebrates and invertebrates. The physiological relation of the single process to the cell body is not clear.

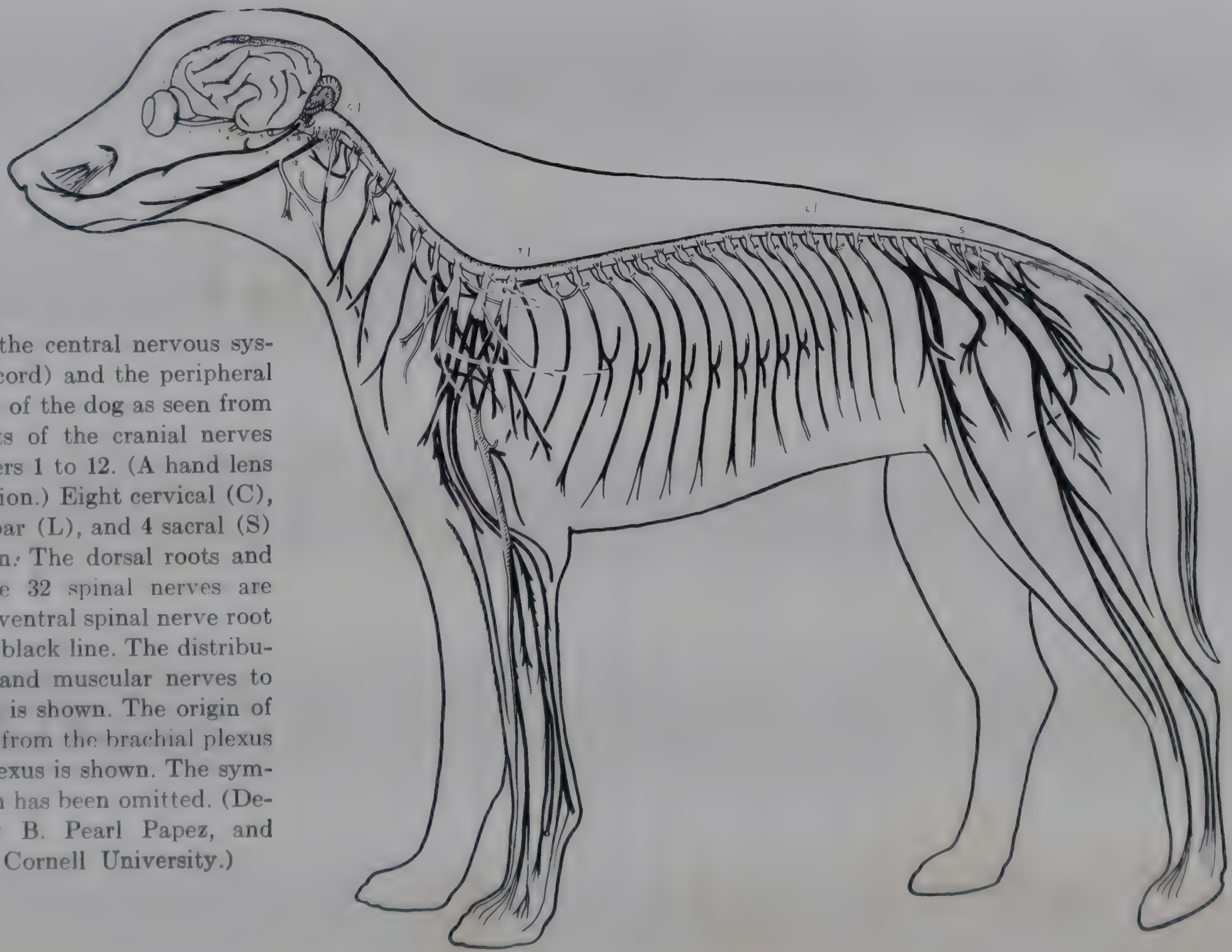

FIG. 132.—Diagram of the central nervous system (brain and spinal cord) and the peripheral somatic nervous system of the dog as seen from the left side. The roots of the cranial nerves are indicated by numbers 1 to 12. (A hand lens will aid their identification.) Eight cervical (C), 13 thoracic (T), 7 lumbar (L), and 4 sacral (S) spinal nerves are shown. The dorsal roots and spinal ganglia of these 32 spinal nerves are drawn in outline. Each ventral spinal nerve root is indicated by a single black line. The distribution of the cutaneous and muscular nerves to the foreleg and hindleg is shown. The origin of these peripheral nerves from the brachial plexus and the lumbosacral plexus is shown. The sympathetic nervous system has been omitted. (Designed and drawn by B. Pearl Papez, and Dr. James W. Papez, Cornell University.)

Bipolar cells have one axon and one dendrite. In vertebrates these cells are well exemplified by the bipolar cells of the retina. These are sensory cells possessing a short axon and dendrite. Similar cells are found in other locations.

In higher vertebrates the nerve cells of the ganglia of the cranial and spinal nerves are embryologically bipolar. However, the two processes later fuse, near the cell body, into one process, so that it presents a T-shaped appearance. One branch of the process becomes an axon of a peripheral afferent nerve fiber, while the other branch passes into the central nervous system by way of the dorsal root of a spinal or cranial nerve. Although both branches are anatomically axons, the peripheral branch is physiologically a dendrite. Such nerve cells may be designated as pseudo-unipolar cells (Maximow). Their function is to conduct nerve impulses centrally. It should be noted that these and all other cells of origin of peripheral afferent nerve fibers are located in ganglia outside the central nervous system. Nerve impulses apparently pass from the peripheral branch to the central branch of these pseudo-unipolar cells without entering the cell body.

Multipolar cells possess numerous branching dendrites and an axon, which may be long or short. Those multipolar cells possessing long axons are designated as Golgi cells Type I. They are typified by the motor nerve cells (motoneurons) in the ventral gray column of the spinal cord. The axons of these neurons emerge from the central nervous system to become peripheral motor nerve fibers. A motor neuron is represented diagrammatically in Fig. 133. Those multipolar nerve cells possessing short axons are designated as Golgi cells Type II. The axons, instead of leaving the gray matter, break up into numerous branches in the vicinity of the cell body. By means of these cells an afferent neuron may be placed into relation with a great many motor neurons. They are therefore designated as internuncial neurons or interneurons.

The Neuron Doctrine. The nervous system is composed of countless numbers of cells known as neurons, together with a certain amount of neuroglial tissue. The latter, however, is not concerned in the performance of nervous functions but acts as an interstitial or supporting tissue. In addition, there is some evidence (Franklin) that neuroglial cells are concerned in the nutrition of the specific nervous elements by acting as intermediaries between the blood and these elements.

That nervous tissue is composed of nerve cells has long been recognized, but knowledge of the significance of these elements and their structural and functional relations is comparatively recent. The doctrine that treats of the status of the neuron in the nerve complex is known as the *neuron doctrine*. It may be summarized as follows:

The nervous system is composed of cells termed neurons. They come in contact with one another at places termed synapses, but there is no protoplasmic continuity between them. The neuron is the functional unit of the nervous system. Only neurons are concerned in performing nervous functions. Chains of neurons constitute the conduction pathways.

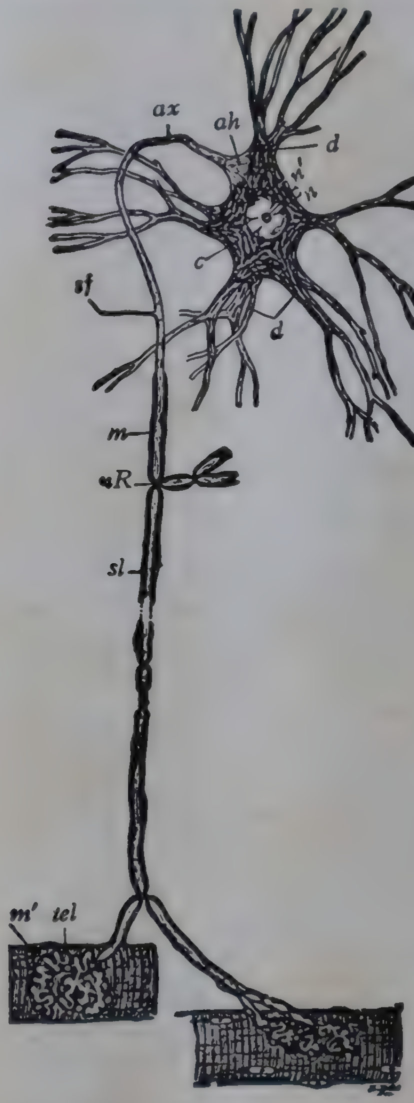

FIG. 133.—Diagrammatic representation of a motor neuron (motoneuron): ah, axon hillock; ax, axon; c, cytoplasm of cell body; d, dendrites; m, medullary sheath; m′, striated muscle fiber; n, nucleus; n′, nucleolus; nR, node of Ranvier; sf, collateral; sl, neurilemma; tel, motor endplate. (Barker, Bailey; from Ranson's *Anatomy of the Nervous System*; copyright —W. B. Saunders Company.)

The Nerve Cell Body. Little precise information is available regarding the physiology of the cell body of the neuron. A good deal is known about its histological peculiarities, but on the whole it is as yet impossible to give these a functional interpretation. That the cell body influences the nutrition of the axon is well known and is indicated by the occurrence of degenerative changes in the axon following its separation from the cell body. The relation of the cell body to the nerve impulses passing through it is a debated point. Many workers believe that the type of conduction in the cell body is similar to the peripheral or axon type of conduction, and that all influences modifying the nerve impulses are derived from the synapse. However, such a view is not universally accepted. Some authorities maintain that the cell body, as well as the synapse, is capable of influencing nerve impulses passing through it. This point of view is apparently exemplified in the relation of the volume of cell-body cytoplasm to the phenomenon of central fatigue in mammalian neurons. Conduction paths that lead through neurons with a large volume of cytoplasm in the dendrites and cell bodies do not tend to show fatigue, whereas those that lead through neurons with small cytoplasmic volume tend to show fatigue. This suggests that the central fatigue of reflex conduction is in part a property of the cell body and dendrites and not exclusively of the synapse (Malone).

Internal Structure. The body of the nerve cell presents many structural features that are similar to those of cells in general. Several of the contained elements, however, may have special physiological significance.

The cytoplasm of nerve cells, including the dendrites, contains a peculiar *chromidial substance*, which in fixed preparations assumes the form of large, sharply outlined, typically arranged masses known as Nissl bodies (Fig. 134, *A*). The discreteness of the chromidial substance is not evident when a fresh nerve cell is examined. Chromidial substance is believed to be made up of nucleoprotein. The presence of Nissl bodies in fixed preparations of nerve cells has long been known, and attempts have been made to show that they are specifically concerned in nerve cell metabolism. What constitutes their special function, if any, is not clear. They are known to undergo lytic changes (chromatolysis) when the nerve cell is fatigued or injured (Fig. 134, *B*). The occurrence of a similar chromidial substance in other kinds of cells is evidence against the view that Nissl bodies are of special importance in nerve cells.

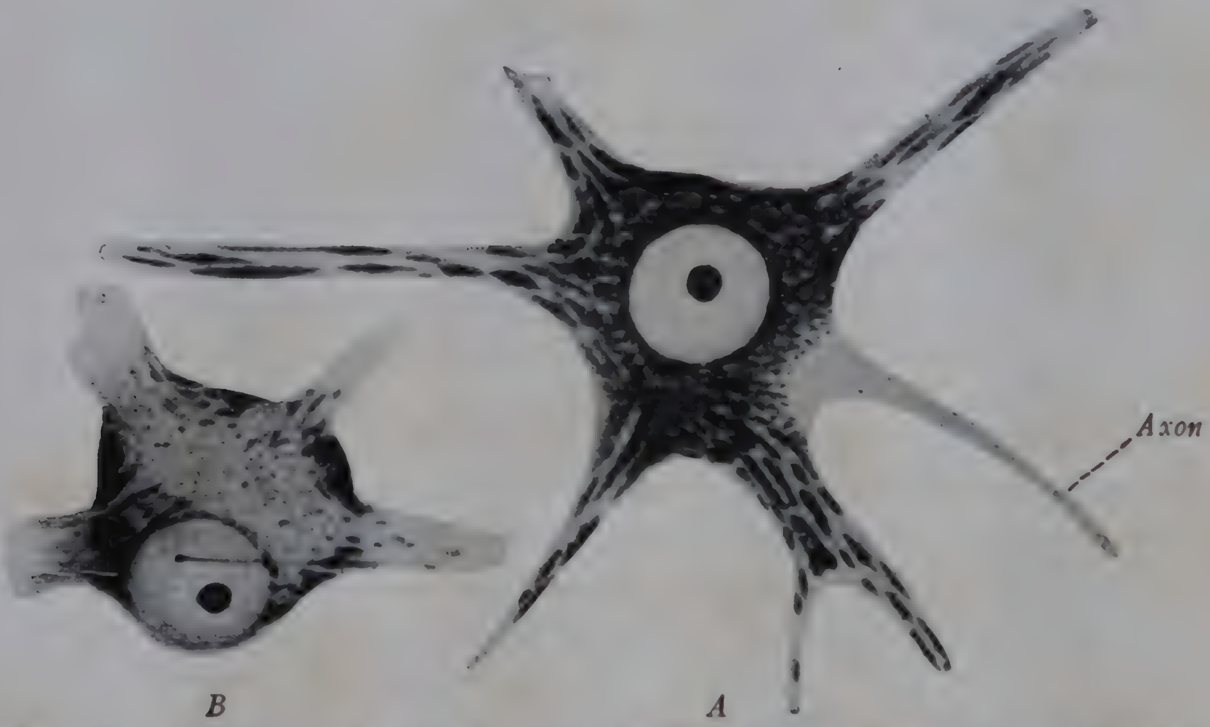

FIG. 134.—*A*, nerve cell from the ventral gray column of the spinal cord of a monkey to show Nissl bodies in the cytoplasm. *B*, nerve cell from the facial nucleus of a dog to show lytic changes in the Nissl bodies following section of the facial nerve. (Schafer; from Ranson's *Anatomy of the Nervous System;* copyright—W. B. Saunders Company.)

Threadlike structures found in all parts of fixed and stained neurons are designated as *neurofibrils*. Whether or not they occur as definite forms in living neurons is not surely known. In the cell body they run in all directions, forming a thick network. Neurofibrils are believed by some to be the ultimate conductors of the nerve impulse, although the evidence for this belief is slight.

DEGENERATION AND REGENERATION IN NERVOUS TISSUE

The number of neurons in the body of mammals is fixed at or near the time of birth, after which time a neuron, if destroyed, cannot be replaced. However, under certain circumstances it is possible for a degenerated peripheral nerve fiber to be quickly and completely replaced. For this to occur, its parent nerve cell body must have remained intact. The cell body, if destroyed, cannot be replaced.

In Peripheral Nerves. When a nerve is transected, the peripheral portion soon alters in appearance and in three or four days loses its ability to conduct nerve impulses when stimulated. The central portion undergoes no grossly apparent change; and when stimulated it is still able to conduct nerve impulses, as is indicated by the production of pain and of reflex contraction of muscles.

Histological studies of the process of degeneration in fibers of peripheral nerves show that the immediate effect of the section is to cause comparatively mild degenerative changes in both the central and peripheral ends of the fiber, known as traumatic degeneration; whereas the more remote effect is to cause grave degeneration in the entire peripheral portion. The latter effect is known as secondary or Wallerian degeneration, named for the British physiologist Waller, who described it in 1850. It takes place because the nerve fiber is completely separated from the cell body, the nutritive center of the neuron. The degeneration finally becomes complete, involving not only the axon but also the myelin sheath, if present. The neurilemma, on the contrary, does not degenerate but undergoes proliferation, as is shown by an increase in the number of nuclei and the amount of cytoplasm. In about seventeen days the neurilemma becomes a syncytium. It is concerned in removing the products of degeneration of the axon and of the myelin sheath. After thirty days or more, all that is left of the nerve fiber is this syncytial neurilemma, known as a protoplasmic or band fiber.

If conditions are favorable, complete regeneration may occur in the degenerated nerve fiber. This is effected under the influence of the cell body. The portion of the axon in connection with the cell body sends out a process along the protoplasmic fiber which finally reaches the termination of the old nerve fiber. This outgrowth becomes the axon of the regenerated fiber. The protoplasmic fiber serves the important function of guiding the new axon to its termination, but it cannot cause the development of an axon. This is possible only under the influence of the cell body and the attached portion of the axon.

The time required for regeneration of the nerve fiber varies with the distance between the severed ends. If the ends are brought close together, regeneration occurs relatively quickly, whereas if they are widely separated, regeneration may require years or may not occur at all. If regeneration does not occur, degeneration of the cell body and its attached stump of axon takes place. A number of workers have estimated the rate of growth of the regenerating fiber down the peripheral part. Clinical evidence in man indicates that the rate is often 2.5 mm. daily, but experimental studies on several mammals indicate rates of 3 to 4 mm. per day (Young). The rates of regeneration of sympathetic fibers, preganglionic and postganglionic, are not very different from those of somatic fibers. Young points out, however, that the rate of advance of the axon tip, the criterion of regeneration usually looked for, is not synonymous with the rate of functional completion of the regeneration. A functionally complete fiber, capable of carrying effective impulses, is obviously required before regeneration can be said to have been accomplished. Much time may elapse between the arrival of the axon tip at its destination and the establishment of *functional* connection.

In Nerve Fibers of the Central Nervous System. Evidence from a number of sources indicates that the nerve fibers of the central nervous system are capable of regenerating, but that the regeneration is usually abortive. However, recent work shows that under some conditions functional regeneration in the central nervous system of mammals is possible, as after transection of the spinal cord in rats. Various explanations have been offered for the rarity with which functional connections are re-established in the central nervous system (Young). The formation of scar tissue in the region of transection is probably a factor. Other mechanical difficulties might be present.

In Nerve Cells. When a peripheral nerve fiber is separated from its nerve cell, more or less severe lytic changes take place in the nerve cell. The chromidial substance tends to become liquefied (Fig. 134, *B*), and the cell shows other evidences of injury. The change in the cell is spoken of as axon reaction. If the injury is not too severe, a new axon grows out from the proximal stump of the old, and finally complete recovery of the neuron occurs.

If the axon is divided close to the cell body, or if the axon stump cannot establish connection with its protoplasmic fiber, or if the neuron is subjected to severe artificial fatigue, the cell body may undergo complete degeneration from which recovery is impossible.

THE SYNAPSE

The synapse is the place where the nerve impulse passes from one neuron to another. At synapses the terminations of an axon, known as terminal knobs or end bulbs, make contact with other neurons. A single nerve cell body is in synaptic connection with many neurons, and one neuron may make synaptic junction with many cell bodies. Since there is lack of protoplasmic continuity at the synapse, it is evident that some sort of membrane or interfacial boundary must exist between neurons. The synapse is regarded as being such a membrane or as owing its peculiar properties to the presence of such a structure. The membrane must be regarded as a living, changing structure and not as a lifeless, static thing. It is a biophysical membrane and might be capable of hindering the movement of ions, accumulating electric charges, supporting potential differences, exhibiting changes of surface tension, manifesting the Donnan equilibrium, etc.

The manner of conduction of the nerve impulse in a nerve fiber varies but little, the only variable being the frequency of the separate impulses. In order to understand many of the peculiar manifestations of the activity of the nervous system, one must therefore look beyond the peripheral nerve fibers into the central nervous system. There the evidence points to the synapse as the principal source of the influence modifying the nerve impulse. Following are some physiological phenomena attributable to the synapse.

1. Although the nerve fiber can conduct a nerve impulse in both directions, a chain of neurons (reflex arc) can conduct in only one direction. In the reflex arc the direction of passage of the impulse is from the afferent neuron through the motor nerve cell into the motor fiber. This is the *law of forward direction.* Stimulation of the motor nerve is quite ineffective in exciting reflex action. The reflex arc is therefore said to be polarized as regards direction of transmission of the impulse. This polarity is believed to be a property of the synapse, whose action may be likened to that of a valve that permits flow in only one direction.

2. Whereas nerve fibers are practically incapable of fatigue, the reflex arc may show quick fatigue. This property is chiefly referable to the synapse, but, as previously noted, it may be in part an attribute of the nerve cell body.

3. The synapse is very susceptible to the action of drugs such as nicotine, strychnine, caffeine, and morphine. (This does not exclude the possibility, however, that at least some of these drugs may act in part on the nerve cell body.)

4. At synaptic junctions, blood capillaries are usually more abundant than at other places in nervous tissue. This and other evidence leads to the belief that the synapse is a seat of high metabolic activity.

5. Such manifestations of reflex action as after-discharge, summa-

tion, inhibition, and reinforcement (p. 602) are probably properties of the synapse.

Newer knowledge on the physiology of the synapse is covered in a monograph by Gasser, Erlanger, Bronk, Lorente de Nó, and Forbes.

RECEPTORS

Receptors are the parts of the nervous machinery of the body concerned in translating ordinary stimuli into nerve impulses. Their essential function is to lower the threshold of excitability of the reflex arc for one kind of stimulus (adequate stimulus) and to raise it for all other kinds (Sherrington). Receptors thus serve to separate out the different stimuli. Receptors are divided physiologically into two principal groups: (1) Those receptors for stimuli originating outside the body, that is, originating in the external environment, are designated as *exteroceptors.* They include the receptors of touch, warmth, cold, and pain found in the skin, and such special receptors as the organs of hearing and vision (distance receptors or teleceptors). They are located in the external surface of the body. (2) Receptors for stimuli originating inside the body—in the internal receptor fields—are termed *interoceptors.* They include *proprioceptors* and *visceroceptors.* The former are located in muscles, tendons, joints, and the vestibular organ. Visceroceptors are located in the alimentary canal, bladder, heart, blood vessels, etc.

Exteroceptors and proprioceptors are sometimes designated as *somatoceptors.* They are concerned in the adjustment of the organism to the external environment. Visceroceptors are concerned in the adjustment of the organism to the internal environment. Examples of nervous reactions involving these three kinds of receptors may now be indicated. (1) If the skin of a limb is pricked the limb is promptly drawn away; an exteroceptor, for pain, has been stimulated and skeletal muscles made to contract reflexly. (2) The tension resulting from the initial contraction of the muscles stimulates proprioceptors in the muscles, tendons, and joints involved, whereupon the further contraction of the muscles is reflexly supported and guided. (3) The presence of food in the digestive tube stimulates visceroceptors, which reflexly call forth the secretion of digestive juices.

Stimulation of somatoceptors does not always excite somatic nervous reactions, nor does stimulation of visceroceptors always excite visceral reactions. Thus cold applied to the skin may cause vasoconstriction—a visceral function; and hunger contractions of the stomach may occasion the contraction of skeletal muscles in an effort to obtain food. This muscular activity is evidently somatic.

Receptors may be classified in another way, depending upon whether or not the nerve impulses aroused reach consciousness. (1) Those receptors that give origin to nerve impulses that arouse sensations are termed sense organs. Examples are the receptors in the skin, eye, and ear. (2) Many receptors give rise to nerve impulses that never reach consciousness but expend themselves in producing reflexes. These receptors may be termed activators. Sometimes the term sense organ is used to include all kinds of receptors, but this is evidently an inexact usage.

Adaptation. Receptors respond to adequate stimuli of threshold intensity or above by setting up a single nerve impulse or, more often, a train of impulses. If the stimulus is applied at constant intensity for a prolonged period, the impulses generated by the receptor diminish in frequency and may disappear completely. This is referred to as *adaptation*. The proprioceptors known as muscle stretch receptors adapt slowly. They are concerned in the antigravity reflex (p. 617) and it is obviously an advantage to the organism that slow adaptation characterizes these receptors. Otherwise the standing reflex would fail. Touch and pressure receptors adapt rapidly. Thus one is usually not aware of the contact of his clothing with the skin and the pressure of a hat on the head is soon forgotten. Pain receptors show little adaptation. The survival value of this is clear. Adaptation of a receptor is not the same as fatigue. For instance, if the stimulus is withdrawn and the receptor is stimulated again, it will respond. This would not be so in the case of a fatigued receptor.

INTENSITY AND QUALITY OF SENSATION

It has already been pointed out that the magnitude of the nerve impulse is not related to the intensity of stimulation, and the form or quality of the impulses does not change with changes in the stimuli. The only variable that a given nerve fiber can conduct is a difference in the frequency of the nerve impulses.

The *intensity* of the sensation aroused in the sensory centers of the cerebral cortex depends on the number of impulses reaching a center in a given time. This is determined by the frequency of the impulses in the fibers that are conducting and upon the number of fibers concerned in transmitting impulses. The first mechanism provides for *temporal summation* of impulses, the second for *spatial summation*. Temporal summation characterizes the responses of the rapidly adapting touch receptors to increasing intensity of stimulation; spatial summation plays a more important part in the action of the slowly adapting muscle receptors.

The *quality* of the sensation aroused depends not upon any differences in how the nerve fibers are stimulated nor upon any differences in the quality of the nerves impulses but upon what nerve fibers are conducting and therefore to what region of the cortex the impulses are carried. If the conduction path transmits impulses to the visual center, light will be perceived regardless of how the impulses are aroused, that is, regardless of how the receptors are stimulated. Light, pressure on the eyeball, or electrical stimulation of the retina can each give rise to nerve impulses that follow the visual path to the visual area in the cerebral cortex, stimulation of which causes a sensation of light. This *doctrine of specific nerve energies* (the term is not particularly good) was proposed originally by Johannes Müller over 100 years ago.

PROJECTION AND LOCALIZATION OF SENSATION

The factors determining the intensity of a sensation and its quality have been briefly considered. In addition, *projection* of the sensation back to the periphery and its *localization* must be mentioned. How these are accomplished is not well understood. The sensation is aroused in the brain, but it is projected back to the periphery (body surface or environmental envelope) and localized at a place which experience has shown to be the source of stimuli when certain nerve cells in the cerebral cortex are excited. Projection and localization are therefore complex psychological functions of the nervous system.

Stimulation of a sensory path at any level will give rise to a sensation which is projected to the periphery. Thus stimulation of the nerve stump, as by pressure from scar tissue, of an amputated limb may give rise to sensations projected back to the "phantom limb."

The accuracy of localization is not equally well developed for all sensations. Cutaneous pain is well localized and so is touch, but other cutaneous sensations are not as well localized.

CUTANEOUS SENSATIONS

As pointed out in Chapter XXI, one of the several functions of the skin is to serve as a sensory surface whereby the organism is brought into intimate relation with its environment. The older physiologists recognized only one cutaneous sensation, touch, in which, however, different attributes could be recognized subjectively. It is now accepted that the skin is endowed with at least four sensations known as touch, cold, warmth, and pain. According to current teaching, these sensations are elicitable from a large number of widely distributed points on the skin known respectively as touch, cold, warm, and pain spots. The receptors for the four cutaneous sensations are commonly assumed to be located in the skin beneath their respective surface spots and to be in functional connection with afferent nerve fibers mediating these senses. However, anatomical knowledge of the peripheral nervous mechanisms of the cutaneous sensations is by no means complete.

Touch. Examination of the skin surface from place to place by gently pressing the end of a light bristle against it reveals that the sensation of touch is not felt uniformly everywhere but most distinctly at certain numerous points termed touch spots. In man these occur in greatest numbers at the finger tips. The adequate stimulus for touch is slight deformation of the surface of the skin, but there is no general agreement as to what structures serve as touch receptors. Tactile corpuscles, found in the dermis, are often assumed to be the receptors, but they are not numerous enough to be the only receptors concerned. Waterston believes that the skin epithelium itself is the receptor for touch, the stimuli excited in these cells being transmitted to the nerve terminals found in the deeper epithelial layers. Merkel's cells in the snout of the pig are probably touch receptors. They are situated in the epithelium.

In addition to this more or less punctate distribution of touch sensation in the skin, it is found that touch is readily and characteristically evoked in hairy regions by bending a hair, provided the movement is great enough to disturb the part of the hair in the follicle. Felt while the hair is actually being bent, touch disappears when the hair becomes static. This is because of adaptation of the nerve endings in the follicle. The appearance and disappearance of nerve impulses when hairs are bent have been studied by detection of the spike potentials of the nerves from the part under investigation. Tactile hairs or vibrissae, so-called feelers, are prominent around the muzzles of some animals.

The sense of touch is not limited to the skin. It is also present in certain mucous membranes, such as those of the oral cavity and the conjunctiva.

Closely related to touch is the sensation of *pressure*. However, it is, for the most part, not a cutaneous sensation but one arising from the stimulation of structures beneath the skin. The Pacinian corpuscles are the receptors.

Temperature Sensations. Examination of the surface of the skin with the point of a warmed metal probe reveals the presence of numerous spots from which a sensation of warmth is obtained. These are termed warm spots. Intervening areas are much less sensitive to warmth. Similiar examination with a cooled probe shows the presence of cold spots, which far outnumber the warm spots. As with the touch spots, it is commonly assumed that in the skin underlying these superficial warm and cold spots are located receptors responsible for translating thermal stimuli into nerve impulses. However, much uncertainty exists as to the histological identity of the warmth and cold receptors.

Pain. By exploration of the surface of the skin with a sharp needle, numerous points can be found from which a sensation of pain can be evoked. These are the pain spots. Careful examination shows that they do not coincide with the other sensory spots of the skin. It is concluded therefore that the sense of pain is independent of the other cutaneous senses. In fact, in some regions—cornea, tympanic membrane—the only sensation present is that of pain. What structures in the skin serve as pain receptors is not known with certainty. It is usually stated that free nerve endings function in this way, there being no specialized receptor. This explains why there is no "adequate" stimulus for pain; the pain receptor is not specialized to respond to one particular form of energy, but will react to several. Heat, chemical irritants, electrical changes, and other potentially harmful stimuli may excite pain endings. Pain endings are sometimes designated as *nociceptors*, since they respond to noxious stimuli.

Itch is believed to result from the weak stimulation of pain endings.

Cutaneous tickle is thought to be an affect arising from simultaneous stimulation of pain and touch receptors.

Cutaneous Sensation and Fiber Size. Nerve fibers can be divided into groups of different conduction velocities, based on the separation of the spike potential of a nerve into different components as it travels along the nerve from the point of stimulation. Conduction velocity and fiber diameter are linearly related to each other. Modern researches on the physiology of receptors and the conduction paths leading from them have yielded information as to the sizes of fibers that conduct impulses giving rise to different sensations. Touch and light pressure activate nerve fibers belonging principally to the beta and delta subgroups of the A group of fibers. Pain giving rise to the sharp sensation of prick is believed to be mediated by the faster-conducting delta fibers of the A group, whereas ache is thought to be mediated by the slower C fibers. The brief nonpainful interval between sharp pain and delayed, dull pain—seen, for example, when one strikes a toe against some object—supports the idea of fast and slow pain. Warmth comes in the fiber "spectrum" just below pain, that is, nerve impulses giving rise to the sensation of warmth are conducted by slower fibers than those for pain. Cold appears in the fiber spectrum just below warmth.

The neural mechanisms of skin sensation are covered in a recent review by Bishop.

THE COMMON CHEMICAL SENSE

The nasal mucous membrane contains two kinds of receptors capable of being stimulated by gaseous substances. One kind, the olfactory receptors, is considered on p. 687. The other kind comprises free nerve endings, probably of the trigeminal nerve, that are stimulated by irritant vapors such as ammonia or hydrochloric acid. As a rule strong reflex manifestations such as sneezing or coughing follow. Further inquiry has shown that in mammals receptors for irritants are not limited to the lining of the nasal passages but are found wherever a mucous membrane comes in contact with the outside. The mouth, eye, anus, and genital orifices all possess such receptors. In amphibians and fishes similar receptors occur all over the exterior of the body. These receptors in mammals are probably a heritage from their primitive aquatic ancestors. Since there is good reason to believe that the receptors for irritants are not identical with those for smell, taste, touch, temperature, or pain, it may be concluded that they are specific receptors mediating a true sense, the common chemical sense.

DEEP SENSATION

Under this heading impulses arising in muscle receptors will be considered. It is common knowledge that the position of limbs in space, the tension of muscles, and the degree of flexion or extension of joints are known to the individual even though the eyes are closed. A blind animal can execute perfectly co-ordinated walking movements.

Nerve impulses from receptors in muscles and tendons pass to the central nervous system and convey the required information. This is sometimes spoken of as "muscle sense." According to Fulton muscles have three kinds of receptors: (1) muscle spindles, (2) tendon organs of Golgi, and (3) Pacinian corpuscles. In addition, free nerve endings mediating pain are found in the blood vessels of muscles and in aponeurotic sheaths. The muscles spindles are stretch receptors, the tendon organs of Golgi are tension receptors, and the Pacinian corpuscles deep-pressure receptors. The spindles are located in the substance of the muscle, the tension receptors in tendons, and the Pacinian corpuscles in tendon sheaths, muscle septa, peritoneum, mesentery, and other places. Proprioceptors in muscles and tendons are referred to again on p. 620.

EFFECTORS

The effectors are the organs of response, and brief reflection is sufficient to show that these come under two general headings: muscle and gland. Muscle may be skeletal (somatic) or visceral. Muscles of the former class, at least in man, are under a high degree of voluntary, intentional, or conscious control, although they often function quite reflexly. They are generally excited through exteroceptive stimulation, but, as previously indicated, they may be aroused by stimulation originating in visceroceptors. Once their contraction is begun, its further course is supported and conditioned by stimulation of proprioceptors. Most visceral muscle is removed from intentional control. It is generally stimulated by impulses originating in visceroceptors, although this is not always true, for exteroceptive stimulation may cause response in visceral muscle. When considering visceral muscle as an effector organ, it must be kept in mind that its fundamental activity is in most instances independent of the central nervous system, that is, automatic.

Glands are visceral organs, and are removed from voluntary control. They are often aroused to activity, so far as the nervous system is concerned, by stimuli originating in visceroceptors, but this is not always the case. A familiar exception is the reflex secretion of sweat in response to the stimulating influence of external heat.

Effector End-Organs. As just stated, effectors are either muscle or gland. Effector end-organs are more or less highly specialized nerve terminations found on effectors or in relation with them. Physiologically it is impossible to differentiate sharply between the end-organ and the effector with which it is related. Both are necessary for the final response. The effector end-organ in some way translates nerve impulse into excitation.

Chapter XXXI

THE SPINAL CORD AND REFLEX ACTION

IF THE spinal cord is transected, it is seen to consist of a central mass of gray matter completely surrounded by white matter. The gray matter consists of nerve cells, dendrites, nonmyelinated fibers, a smaller number of myelinated fibers, blood vessels, and neuroglia. The white matter consists chiefly of longitudinally running myelinated nerve fibers, supported by neuroglia. Closely investing the spinal cord there is a highly vascular covering known as the pia mater. Along the median line of the dorsal of the cord extends the deep dorsal median sulcus, while along the median line of the ventral surface is found the much shallower ventral median fissure.

Funiculi. The white matter of the spinal cord is divided anatomically into several columns of nerve fibers known as funiculi. Occurring on each side, these funiculi are designated as dorsal, lateral, and ventral. The dorsal funiculus extends from the dorsal median sulcus to the line of origin of the dorsal roots of the spinal nerves; the lateral funiculus, from the line of origin of the dorsal roots of the spinal nerves to the similar line of the ventral roots; the ventral funiculus, from the line of origin of the ventral roots to the ventral median fissure. Each funiculus is limited centrally by the gray matter.

Gray Columns. The gray matter, completely surrounded by white matter, extends throughout the length of the spinal cord in an unbroken column. In cross-section it has the general shape of the letter H. The ventral part of each lateral mass of gray matter is designated the ventral horn or column; the dorsal part, the dorsal horn or column. From the lateral side of the ventral column projects the lateral column. The connection between the two lateral masses of gray matter is known as the gray commissure. It contains the central canal. Under the gray commissure is the white commissure.

Nerve Cells of the Spinal Cord. The nerve cells of the spinal cord are multipolar, and each cell possesses a single axon. Four groups of nerve cells have been distinguished. (1) Cells with short axons which do not leave the gray matter are found in the dorsal column. They are Golgi cells Type II. Their number in the spinal cord of higher animals is relatively small. (2) Large motor nerve cells are situated in the ventral column. They possess long axons, which leave the spinal cord in the ventral roots of the spinal nerves to pass to the skeletal muscles. These neurons are designated as motoneurons, and their cells of origin are most abundant in the cervical and lumbar enlargements of the spinal cord. One motoneuron may innervate as many as 165 muscle fibers. To accomplish this, the axon branches extensively after entering the muscle (p. 560). (3) Small cells are located in the lateral column of gray matter in the thoracic and upper lumbar regions. Each cell gives off an axon, which leaves the spinal cord in the ventral roots as a preganglionic fiber of the sympathetic nervous system. (4) Small or medium-sized cells, interneurons, present chiefly in the dorsal column, give off axons that pass into the white matter, where they run up or down the cord, or divide into ascending and descending branches. Some of the fibers run all the way to the brain; others connect contiguous or more distantly situated spinal segments. Collateral and terminal branches of fibers of the latter enter the gray matter, where they end around nerve cells. Those that terminate in the side of the cord from which they arise are designated as association fibers; those that terminate in the opposite side of the cord, by passage through the white commissure, are called commissural fibers. These fibers make up the fasciculi proprii (p. 598).

The facts just stated make it evident that the sensory cells of the spinal cord are grouped in the dorsal gray column, while the motor cells are grouped in the lateral and ventral columns. The sensory cells of the dorsal column are the primary sensory centers, or terminal nuclei, of the dorsal roots fibers, whereas the cells of the lateral and ventral columns are the primary motor centers, or nuclei of origin, of the ventral root fibers. However, some of the dorsal root fibers have their terminal nuclei in the medulla (nucleus gracilis and nucleus cuneatus).

FUNCTIONS OF THE SPINAL CORD

The spinal cord has two main functions: (1) it is the seat of many reflex centers controlling the muscles of the trunk and limbs; (2) it is a path of conduction between these centers and the correlation centers of the brain. The first function is more primitive and is therefore found to be of great importance in lowly vertebrates such as the frog. In the higher vertebrates, especially man, the other function is of first importance. These functions will be studied under three headings: (1) the fiber tracts, (2) reflex action and the spinal animal, and (3) the conduction pathways between the cord and brain.

FIBER TRACTS OF THE SPINAL CORD

The white matter of the spinal cord is composed of nerve fibers. Those possessing similar functions, origins, and terminations are grouped together in fairly definite bundles called tracts. Certain groups of nerve fibers located in the same general region of the cord but possessing different functions are called fasciculi. They are mixed bundles of fibers.

The tracts of the spinal cord are divided into ascending and descending tracts. Some are short, connecting adjacent segments of the cord; others are longer, connecting more remote levels of the cord; still others extend from the cord to the brain or from the brain to the cord. The tracts are usually designated by a compound word formed from the names of the places of origin and termination of the tract, the name of the place of origin coming first in the compound word.

As they run up the cord, the ascending tracts gain fibers from successive groups of nerve cells around which the dorsal root fibers terminate, or from branches of the dorsal root fibers themselves, and therefore becomes larger. As they travel down the cord, the descending tracts give off fibers that end in relation to motor nerve cells in successive segments of the cord and therefore become smaller.

Knowledge regarding the fiber tracts of the spinal cord of the large domestic mammals is, for the most part, meager. More information is available for the small mammals. The accompanying list of tracts is not complete. Only the more important ones are given. Their location in the cord (man) is shown diagrammatically in Fig. 135. See also Figs. 139 and 141 (pp. 619 and 636), which show a number of the descending tracts, and Fig. 142 (p. 637), which shows several of the ascending tracts, in the dog. These figures should be studied in connection with the discussions to follow.

Ascending Tracts. *Fasciculus Gracilis and Fasciculus Cuneatus.* These are mixed bundles occupying much the greater part of the dorsal funiculus. The fasciculus gracilis is medial to the fasciculus cuneatus. They are made up principally of the ascending branches of the dorsal root fibers. The fibers in the gracilis come from the sacral, lumbar, and lower thoracic nerves; those in the cuneatus, from the upper thoracic and cervical nerves. These fasciculi terminate in their respective nuclei in the medulla, from whose cells axons arise to pass, in a tract known as the medial lemniscus or fillet, to the thalamus of the opposite side. Third axons arise from cells in the thalamus and run to the cerebral cortex. These fasciculi convey impulses concerned in proprioceptive reflexes, and in the sensations of posture, spatial judgment, and the like, which may give rise to conscious reactions. They also mediate to some extent touch and pressure sensations. They are best developed in primates (Weil), although they are present in all mammals.

Dorsal Spinocerebellar Tract. The fibers of this tract arise from the cells of the nucleus dorsalis on the same side and pass to the cerebellum by way of the posterior peduncle or restiform body. The tract conveys proprioceptive impulses from muscles and tendons of the limbs. It does not respond to the stimulation of cutaneous afferent fibers. The velocity of the nerve impulses conducted in this tract is high. The tract is found in the dorsolateral part of the lateral funiculus and is especially well developed in Ungulata, as indicated by the size of the restiform body (Weil).

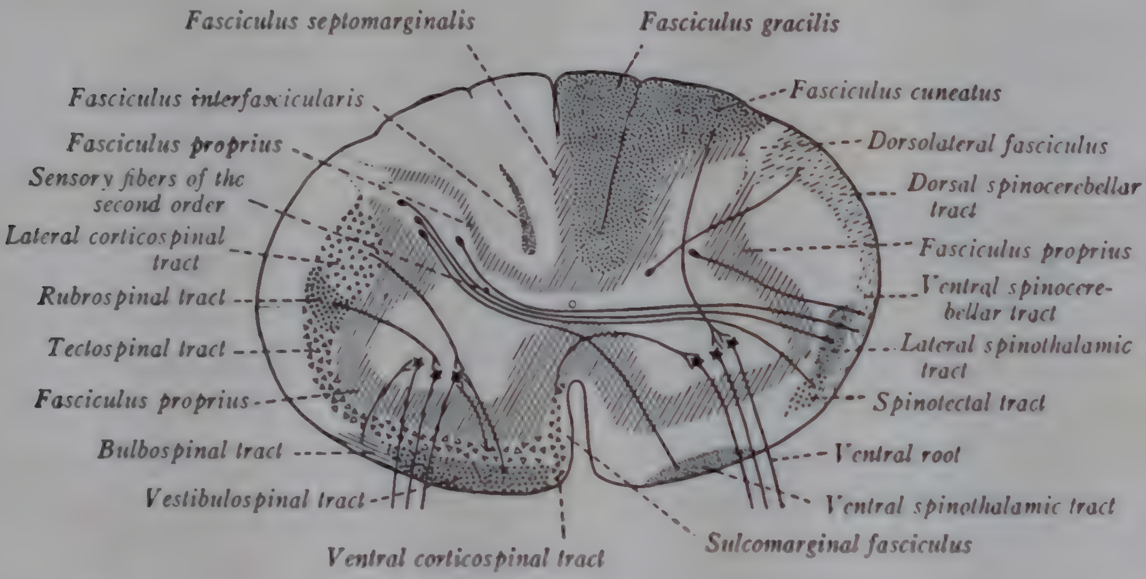
Fasciculus septomarginalis
Fasciculus gracilis
Fasciculus interfascicularis
Fasciculus cuneatus
Fasciculus proprius
Dorsolateral fasciculus
Sensory fibers of the second order
Dorsal spinocerebellar tract
Lateral corticospinal tract
Fasciculus proprius
Rubrospinal tract
Ventral spinocerebellar tract
Tectospinal tract
Lateral spinothalamic tract
Fasciculus proprius
Spinotectal tract
Bulbospinal tract
Ventral root
Vestibulospinal tract
Ventral spinothalamic tract
Sulcomarginal fasciculus
Ventral corticospinal tract

FIG. 135.—Diagram of the chief fiber tracts of the spinal cord of man. On the right, the ascending tracts are represented; on the left, the descending tracts. For certain differences in animals, see text. (From Ranson's *Anatomy of the Nervous System*; copyright—W. B. Saunders Company.)

Ventral Spinocerebellar Tract. The fibers of this tract originate from nerve cells in the dorsal column, on the same and opposite sides, and enter the cerebellum by way of the anterior peduncle. It conveys proprioceptive impulses from the trunk musculature. It is found in the ventrolateral part of the lateral funiculus.

Spinothalamic Tracts. The *ventral* spinothalamic tract, found in the ventral funiculus, consists of fibers that originate from nerve cells in the dorsal column of the opposite side and cross the median plane in the white commissure. The fibers end in the thalamus in synaptic relation to nerve cells from which axons arise to pass to the cerebral cortex.

The *lateral* spinothalamic tract consists of fibers that originate from nerve cells in the dorsal column on the opposite side and run in the lateral funiculus. The tract ends in the thalamus. From nerve cells in this organ axons arise and pass to the cerebral cortex.

The spinothalamic tracts conduct nerve impulses which mediate the following kinds of sensation (Ruch): pressure and touch (in part), pain in cutaneous, muscular, and visceral regions, warmth and cold, cutaneous tickle, itch, muscular fatigue, bladder and sexual sensations.

Descending Tracts. The descending or motor tracts connect different parts of the brain with the spinal cord. Some of them originate in the cerebral cortex, whereas others originate at various reflex centers in the brain-stem.

Corticospinal Tracts of Man. These are the most important descending tracts in man. Constituting the only direct motor connection between the cerebral cortex and the spinal cord, they place the motoneurons, and thus the skeletal muscles, under cerebral control. There are two corticospinal tracts—lateral and ventral—on each side. It was formerly believed that the fibers of this tract originated exclusively from the large pyramidal cells of the motor area of the cerebral cortex. Recent work (Fulton) makes it evident that only a small percentage of the fibers originate in this way. Motor cells in other regions of the cortex contribute many fibers to the corticospinal tract.

The lateral corticospinal tract, known also as the crossed pyramidal, is located in the lateral funiculus. It is composed of fibers that originate on the opposite side of the cerebral cortex and cross the median plane in the decussation of the pyramids. It comprises most of the fibers of the corticospinal system. The tract gradually ends, by collaterals and terminations, in relation to the motoneurons of the ventral column. Recent work indicates that an interneuron is placed between the terminations of the fibers and the motor cells. The ventral corticospinal, or direct pyramidal, tract is composed of those corticospinal fibers that do not cross in the medulla oblongata. It is much smaller than the crossed tract and is found in the ventral funiculus. Its fibers terminate like those of the lateral corticospinal tract, but before ending they cross to the opposite side of the cord in the white commissure. The tract disappears near the middle of the thoracic region of the cord.

In man approximately 50 per cent of the fibers of the pyramidal tract terminate in the cervical segments of the cord, 20 per cent in the dorsal segments, and 30 per cent in the lumbar segments (Weil and Lassek).

It may be emphasized that all the corticospinal fibers originate from the cortex on the side *opposite* to that on which they end in the cord. The right cortex therefore controls the muscles of the left side of the body, and the left cortex those of the right side.

Corticospinal Tract of Animals. The corticospinal tract is phylogenetically young and marked variations in its size and position occur. An article by Simpson contains a review of the older literature on the pyramidal tract of animals. King made a study of the corticospinal tract in the sheep. The evidence indicated that the tract in this animal is in a primitive state of development, for it could not be traced farther back than the first cervical segment. Destruction of the motor areas in the cerebral cortex did not result in serious disturbances of skeletal muscle movement, even just after the operation. In the light of subsequent work on the corticospinal tract, there is no certainty that all the cells of origin of the tract were destroyed in King's experiments.

Lassek has made a study of the number and size of fibers making up the pyramidal tract of six ungulates (cow, goat, sheep, pig, mule, deer). The level at which the study was made was the upper part of the medulla oblongata. As judged by the number of fibers present, the tract at this level is well developed in the animals studied. In the different animals the number of fibers ranged from about 200,000 to about 500,000. The figure for man is about 1,000,000 fibers.

The pyramidal tract shows a relatively low conduction velocity. In the cat the velocity in the different fibers ranges from 18 to 65 meters per second (Lloyd).

That the corticospinal tract places the motoneurons under cortical control seems certain, but there is no general agreement as to the nature of the control. Some think that the tract is the conduction pathway for volitional and acquired movements. Others believe that it supplies tone to the motoneurons. Another line of evidence suggests that it exerts an important effect on the interneurons and thus, perhaps, on *afferent* impulses to all levels of the central nervous system. It is conceivable that all of these functions are subserved by the tract. Perhaps the pyramidal tract has different functions in animals of different phylogenetic development. However, Lassek makes the following statement: "On the basis of what is known, no tract in the central nervous system changes in its basic physiology as the mammalian phylogenetic scale is ascended."

Rubrospinal Tract. This tract sends some of its fibers back as far as the sacral region. Its fibers originate from the red nucleus of the midbrain and immediately after leaving the nucleus they cross the median plane. They end in synaptic relation with the motoneurons of the ventral column. The fibers of the rubrospinal tract convey impulses from the cerebellum, vestibular nuclei, corpus striatum, and premotor area to the motoneurons. The tract is not well developed in man but is important in most of the lower mammals. It, or a similar tract, is prominent in the sheep. In this same animal there is another well-developed descending tract located in the ventral part of the ventral funiculus. It extends back as far as the sacral region. Its fibers end in direct relation with the motor cells of the ventral gray column (King). The rubrospinal tract is phylogenetically old.

Tectospinal Tract. Located in the ventral funiculus, this tract originates from the roof, or tectum, of the midbrain (anterior colliculus) and ends in the ventral gray column of the spinal cord. Some of the fibers cross in the dorsal tegmental decussation. The fibers conduct to the motoneurons of the muscles of the trunk and limbs impulses concerned in optic and auditory reflexes.

Vestibulospinal Tracts. Of the two vestibulospinal tracts, the crossed one arises in the medial and spinal vestibular nuclei of the medulla and the direct one in the lateral vestibular nuclei of the pons. They end in the ventral gray column, some of the fibers extending back as far as the lower lumbar region of the spinal cord. The tracts conduct to the motoneurons impulses from the vestibular organ and cerebellum that are concerned with inhibition of the antigravity reflex.

Reticulospinal Tracts. These tracts, two in number, are composed of fibers that conduct impulses from nerve cells grouped into small masses or scattered in the reticular formation in the upper part of the pons and the lower part of the midbrain. They terminate, probably through interneurons, in relation to nerve cells in the intermediolateral and ventral columns of gray matter. Thus impulses would be transmitted to the periphery via the sympathetic system and via the motoneurons. Impulses over the latter path probably aid in the maintenance of tone of skeletal muscle.

Fasciculus Proprius. Surrounding the gray matter are numerous short ascending and descending fibers constituting the fasciculi proprii or ground bundles. These fibers begin and end in the gray matter and connect the different segments of the cord. They are concerned in intersegmental spinal reflexes. A fasciculus proprius is found in each funiculus.

REFLEX ACTION: THE SPINAL ANIMAL

A reflex act is the involuntary production of activity in some effector (muscle, gland) by the stimulation of a receptor. The simplest reflex arc or circuit consists of a receptor, an afferent neuron, an efferent neuron, and an effector, or organ of response. The minimum theoretical number of neurons in the reflex arc is therefore two. However, it may be doubted if reflex arcs of this simplicity are ever employed in carrying on nervous function. Usually many neurons are involved. One afferent neuron makes many central connections, thus bringing about *divergence* of a path. One motor neuron receives impulses from many other neurons by reason of *convergence* of paths.

The neuron is the structural basis of the nervous system, and it is often said also to be the functional basis. Since, however, a single neuron is never concerned in performing nervous functions, it is evident that the reflex arc in its various forms constitutes the real physiological basis of nervous function.

The statement that a reflex act is an *involuntary* act may be emphasized. The so-called voluntary acts are not included in the reflexes; but the fundamental nervous mechanism of the production of the two kinds of acts is similar. Although all reflexes are performed involuntarily, many are accompanied by or followed by reactions in consciousness. Thus when the skin comes in contact with a hot object, the limb is reflexly drawn away; but the animal is conscious of pain because of the conduction of impulses to higher levels of the nervous system. Acquired movements requiring great skill, as piano playing, are not reflexes. They belong to the group of acquired automatisms. Reflexes (the unconditioned reflexes of Pavlov) belong to the nervous organization with which an animal is equipped at birth; they are inborn and transmitted by heredity. In some instances they develop only fairly late in life, nevertheless they are innate.

Although the true reflexes take place through the spinal cord and brain-stem, the cerebral cortex exercises control over many of them. Therefore in order to study reflexes uncomplicated by cortical control or interference, it is necessary to separate from the cerebrum the part of the nervous system to be studied. If the spinal cord is separated from the brain, a *spinal animal* results, and in this greatly simplified nervous system reflex activity can be studied. The nervous mechanisms that remain functional in such an isolated spinal cord are the afferent neurons, the interneurons of the fasciculi proprii, and the efferent or motor neurons.

The spinal frog is admirably adapted to the study of reflexes. For several minutes after the brain is destroyed, the frog remains limp and reflex activity of the cord is absent. This condition of *spinal shock* soon disappears, and response to peripheral stimulation returns. The frog, motionless when not subjected to peripheral stimulation, shows muscular contraction when the skin is stimulated: if a toe is pinched, the leg is drawn up; if acid is applied to the skin, an attempt is made to scratch it away; if the warmth receptors are stimulated, vigorous contractions may occur.

Spinal mammals may also be prepared. However, spinal shock is a much more serious condition in the mammal than in the frog and a much longer time is required for its disappearance. It is therefore often an advantage in studies of the spinal mammal to use the "chronic" spinal preparation. In order for the phrenic innervation to remain and breathing therefore to continue, the transection in the survival spinal preparation must be below the fifth cervical segment. If transection is made at a higher level, as in the usual acute preparation, artificial respiration must be provided.

The nature of spinal shock has been studied by many workers, but no fully satisfactory explanation of the condition is available. In spinal shock in the mammal the extensor reflexes are depressed but the flexor reflex is usually present in distinct form even just after the transection. The most acceptable view regarding spinal shock is that nerve impulses which normally descend from some supraspinal level to the spinal cord and maintain its motor nuclei in a normal state are cut off. This effect is believed to be transmitted from the medulla to the spinal cord via the vestibulospinal tract and perhaps other paths. It *facilitates* the motoneurons that govern the extensor muscles and *inhibits* the motoneurons controlling flexor muscles. Upon transection of the spinal cord these effects are cut off, whereupon depressed extensor and exaggerated flexor reflexes occur. After a time the condition of spinal shock disappears and the action of the spinal motor centers becomes more normal.

If the neuraxis is transected in the region of the midbrain, a bulbospinal (decerebrate) animal results, in which there is great exaggeration of the standing reflex, the extensor muscles showing strong contraction. The vestibulospinal tract is released from inhibitory control. This condition, known as decerebrate rigidity, is discussed elsewhere (p. 617). The books by Sherrington and Creed and associates contain the results of comprehensive studies of the spinal reflex mechanism. While many reflexes take place through the spinal cord, it is not the only seat of reflex action. The brain-stem, to be studied in another chapter, is also an important seat.

Possible Combinations of Neurons in Reflex Arcs. It has been pointed out (Herrick) that neurons may be so combined and compounded as to give at least five types of reflex arcs. It should be understood, however, that the neuronal mechanisms actually employed are much more complicated than any of those here described and illustrated. Following are the types:

1. The simplest reflex arc imaginable would consist of two neurons (Fig. 136, *1*).

2. Several simple reflex arcs may be united in series so as to give a chain of reflex arcs (Fig. 136, *2*). Activity in the first simple arc stimulates activity in the second, which in turn stimulates the third, and so on. Probably many of those complex nervous reactions known as instincts are chain reflexes.

3. Neurons may be so compounded in the reflex arc that stimulation of one receptor causes response in one or both of two effectors (Fig. 136, *3*). The afferent neuron is thus in synaptic relation with two efferent neurons. If the effectors can co-operate in the production of the response, the mechanism is similar to that of the simple reflex, but the response is more complicated. Such a reflex is designated as an allied reflex. If the effectors produce opposite effects, such as are produced

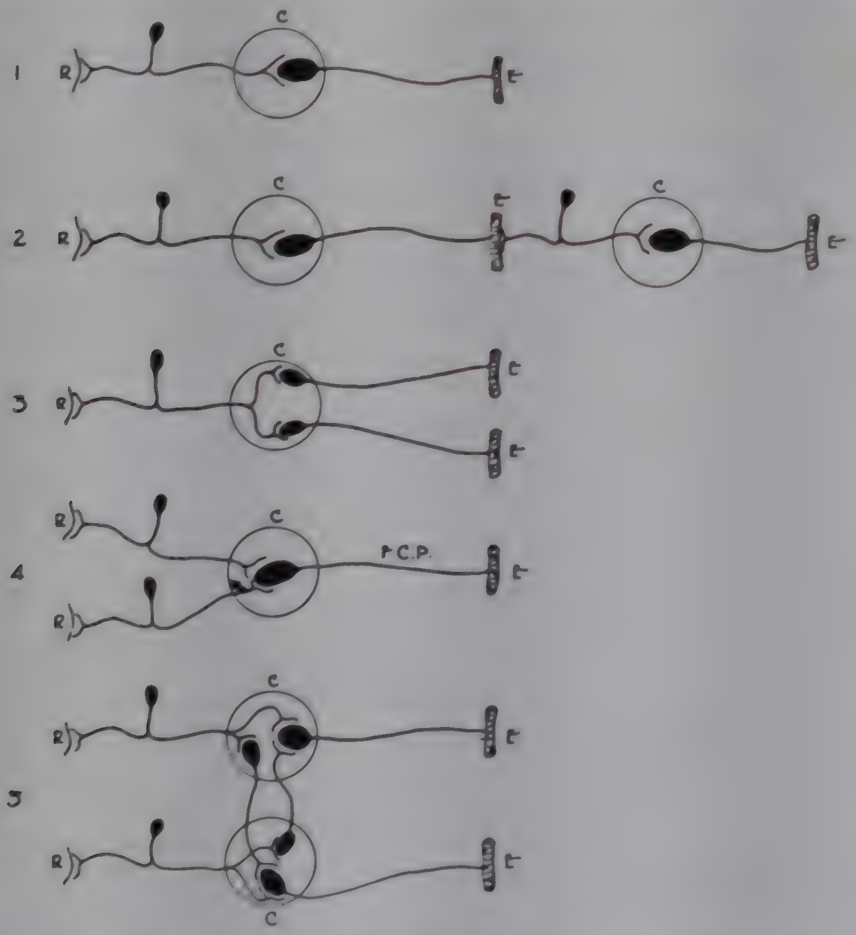

FIG. 136.—Diagrams showing the relations of neurons (simplified) in various types of reflex arcs: 1, simple reflex; 2, chain reflex; 3, arrangement illustrating either allied or antagonistic reflex and showing divergence; 4, arrangement illustrating either allied or antagonistic reflex, final common path (F.C.P.), and convergence; 5, arrangement illustrating reflexes involving correlation. R, receptors; C, centers; E, effectors. (Modified from Herrick.)

the motoneurons to discharge and a reflex to be executed. It is supposed that *spatial summation* occurs in such cases. The first volley causes an excitatory state to be set up on the surface of a neuron, which spreads some distance from the place where the functioning terminal knob contacts the nerve cell body of the next neuron. Another volley arriving within the period of the excitatory state would create an effect which would be summated with the previous effect and the motoneuron would fire. Spatial summation could occur if the impulses arrived simultaneously or at any time during the existence of *c.e.s.* *After-discharge* means the continued firing of the reflex center after the external stimulus has ceased to act. It is believed to be the result, at least in part, of the fresh building up of *c.e.s.* by the continued arrival at the motoneurons of excitatory impulses from interneuronal paths of various lengths, complexity, and conduction speeds. A sort of reverberation in the central nervous system occurs.

The intimate nature of *c.e.s.*, upon which after-discharge depends, is not known. Probably depolarization of the parts of the surface of the motoneuron cell-body underlying and adjacent to the terminal knobs is a factor. The arrival of the next impulse or volley of impulses would find the stage set for effective action. It was at one time thought that excitatory chemical substances released at the synapses, for example, acetylcholine, might account for *c.e.s.*, but this view is not now generally held.

Central Inhibition and Reciprocal Innervation. When two groups of muscles are so situated that they act in opposite ways on the same structure, they are said to be antagonists. The extensors and flexors of the limbs are good examples of antagonistic muscles. When one muscle contracts, any contraction of its antagonist must be inhibited if effective results are to follow. Inhibition of the antagonist is effected *centrally* and not peripherally, for skeletal muscle, unlike cardiac muscle and some other visceral muscles, does not possess inhibitory nerves. Inhibition is brought about by the cessation of discharge along the motoneurons. Many experimental facts about central inhibition are known (Creed and associates, Fulton), but the nature of the inhibitory process is unknown. The humoral theory, in which it was postulated that some inhibitory chemical substance is released at the synapse or elsewhere in the centers, has now largely been abandoned. The trend of modern opinion is that the process, whatever it is, probably has its parallel in the action of peripheral nerve. A suggestion or two, based on the literature, may be given. One form of central inhibition may be the result of polarization effects at the surface of the cell bodies of the motoneurons. A period of subnormal response in peripheral nerve has been demonstrated and the suggestion has been made that central inhibition is an analogous condition.

The inhibition of a flexor muscle when the extensor is contracting and the inhibition of an extensor when a flexor is in action illustrate what has been termed *reciprocal innervation* of antagonistic muscles. In the spinal reflexes, shortly to be considered, and in locomotion, the mechanisms of reciprocal innervation must be called into use.

SPINAL REFLEX MECHANISM

The nerve fibers of the dorsal roots of the spinal nerves are afferent, while those of the ventral roots are efferent. These facts are now so well established that they are often referred to as the *Bell-Magendie law*,[1] named after the independent workers who made the basic observations early in the last century. The cells of origin of the dorsal root fibers are located in the dorsal root ganglia; those of the ventral root fibers, in the ventral and lateral gray columns. According to the theory of neural components, the nervous system may be divided into functional components as follows: somatic afferent, somatic efferent, visceral afferent, visceral efferent. The somatic components are concerned chiefly in the regulation of the somatic mechanisms of the body. The visceral components are concerned mainly in the regulation of the visceral mechanisms. However there is a good deal of physiological overlapping on the afferent side.

The afferent fibers of the spinal nerves are either somatic or visceral. The somatic afferent fibers are either exteroceptive, coming from the skin, or proprioceptive, coming from muscles, tendons, and joints. The visceral afferent fibers are interoceptive. The efferent fibers of the spinal nerves are either somatic or visceral. The somatic efferent fibers innervate skeletal muscle. The visceral efferent (autonomic) fibers supply visceral muscle and glands (Fig. 137).

After entering the spinal cord all afferent nerve fibers establish two kinds of connections: (1) for intrinsic reflexes of the cord, and (2) for the conduction of their impulses to the brain.

Intrinsic Spinal Reflexes. The simplest possible reflex arc consists of two neurons, afferent and efferent. It may be doubted, however, whether reflex arcs consisting of only two neurons actually exist. In the spinal cord an interneuron, or a chain of such neurons, is interposed between the afferent and efferent neurons. Its function is to bring the afferent neuron into relation with many efferent neurons

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[1] Apparent exceptions to the Bell-Magendie law have been announced from time to time, but most of them have not been supported by further work. The possible existence of dorsal-root efferent vasodilator fibers is mentioned elsewhere (p. 179), but the matter is still unsettled.

located at different levels and on one or both sides of the cord. These interneurons belong to the fasciculus proprius system (p. 598). When it is considered that the dorsal root fiber gives origin to ascending and descending branches, that these give off numerous secondary branches, each of which may end in synaptic relation with an interneuron, and that each interneuron may be in physiological connection with other interneurons or motor neurons, it is evident that nerve impulses in one afferent neuron may arouse activity in innumerable motor neurons. It may be stated as probable that each afferent neuron is in potential functional connection with all motor neurons of the spinal cord. However, such diffuse connection as this is not called into use under physiological conditions; but in strychnine poisoning all these avenues may be open. A reflex arc involving one segment of the spinal cord is shown diagrammatically in Fig. 138.

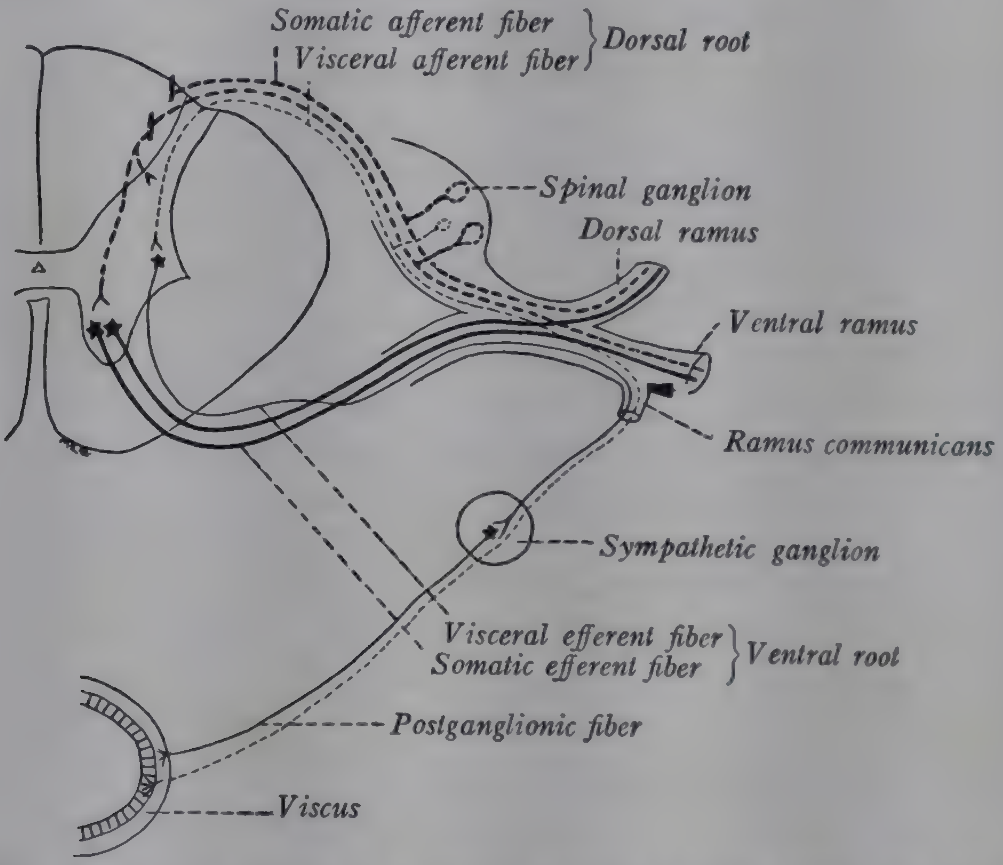

Somatic afferent fiber
Visceral afferent fiber
Dorsal root
Spinal ganglion
Dorsal ramus
Ventral ramus
Ramus communicans
Sympathetic ganglion
Visceral efferent fiber
Somatic efferent fiber
Ventral root
Postganglionic fiber
Viscus

FIG. 137.—Schematic diagram of a section through a spinal nerve and the spinal cord to show the functional components of the nerve. (From Ranson's *Anatomy of the Nervous System*; copyright—W. B. Saunders Company.)

Following are some of the reflexes elicitable in the spinal animal. The *knee-jerk* is a reflex induced by a light blow struck on the patellar tendon. The knee-jerk of the spinal animal is a short tetanus. The reflex results apparently from stimulation both of tension and stretch receptors. Other tendon-jerks are elicitable. The *flexor reflex* is a contraction of the flexor muscles of the hind limb caused by stimulation of any sensory nerve of the limb. All the joints are involved. This reflex is likewise a short tetanus. It is well defined in the spinal animal, usually right after spinal transection as well as later. In the intact animal this reflex is generally a nociceptive response, that is, a reaction to a harmful stimulus. The *extensor thrust* is a reflex in which strong brief extension of the homolateral hind limb results from pressure to the foot pads or from quick separation of the toes. This reflex comes into play in locomotion, especially at fast speeds where thrust of the limb against the ground is required. The reflex is also probably concerned in expelling foreign bodies from between the toes. The *crossed extensor reflex* is more complicated than any of the foregoing. It is called forth by stimulation of any sensory nerve of the contralateral hind limb. It is an attitudinal reflex and will be referred to again under the postural reflexes (p. 621). In the intact animal this reflex prevents the body from sinking under gravity when the opposite limb is raised by a flexion reflex. The *scratch reflex* (dog) is evoked by stimuli applied to the skin in a saddle-shaped area on the back, side, and flank. This reflex consists of a scratching movement of the homolateral hind limb, the frequency of the flexions being about four per second. The spinal animal even shows under certain conditions of stimulation a definite *stepping reflex*. In fact, as pointed out by Sherrington, much of the reflex activity of the limb of the spinal dog is adapted to locomotion.

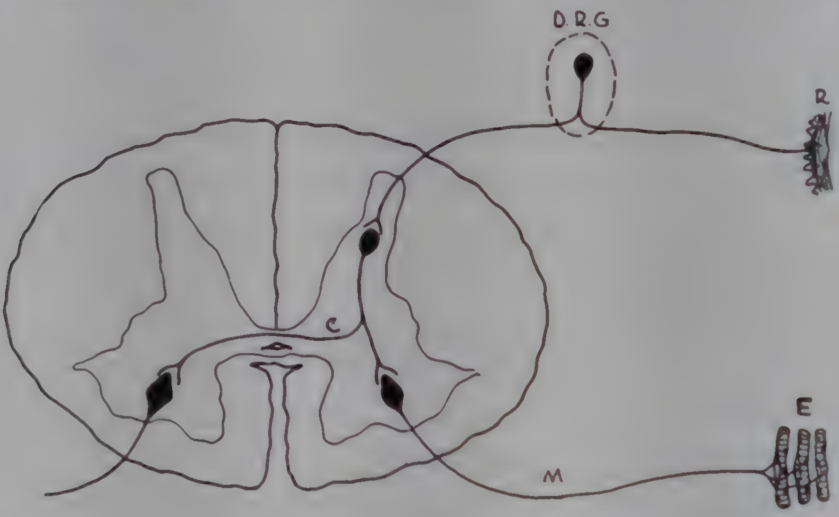


FIG. 138.—Diagrammatic representation of a reflex arc involving one segment of the spinal cord. R, receptor; D.R.G., dorsal root ganglion; C, correlation neuron (interneuron), making possible a crossed reflex; M, motor neuron; E, effector (skeletal muscle).

If a quiet animal (dog, cat) is chosen and care is taken not to excite it, practically all of the foregoing spinal reflexes can be elicited in the fully intact animal. However, a detailed experimental analysis of the reflexes cannot be made in this way.

CONDUCTION PATHWAYS BETWEEN THE SPINAL CORD AND BRAIN

The fiber tracts in the spinal cord have already been studied. It now remains to view these tracts as parts of physiological conduction pathways between the spinal cord and brain.

Afferent Systems. As previously stated, all afferent nerve fibers entering the spinal cord establish connections for intrinsic reflexes and for the conduction of impulses to the brain. The conduction pathways are made up of fibers bearing impulses from the proprioceptive and exteroceptive fields.

Proprioceptive Pathways. Nerve impulses originating in the proprioceptive field travel by one of two pathways to the brain. If the impulse is destined for the cerebral cortex, its conduction fiber, entering the cord via the dorsal root, finds its way into the dorsal funiculus and passes to the medulla oblongata in either the fasciculus gracilis or fasciculus cuneatus. In the nucleus of one or the other of these fasciculi the fiber terminates. A second neuron then continues the pathway, in the medial lemniscus, to the thalamus of the opposite side, from which a third neuron runs to the cerebral cortex (Figs. 141, 142; pp. 636, 637).

Fibers conducting proprioceptive impulses destined for the cerebellum enter the spinal cord in the usual way but terminate around nerve cells of the dorsal gray column. Fibers arising from these cells enter the dorsal or ventral spinocerebellar tract and pass to the cerebellum.

Exteroceptive Pathways. Fibers from the exteroceptive field (touch and pressure, pain and temperature) enter the spinal cord in the dorsal roots and almost immediately penetrate the gray matter where they terminate in relation with neurons of the second order in the dorsal column. Axons arising from these nerve cells cross to the opposite side of the cord, and enter either the ventral spinothalamic or the lateral spinothalamic tract. They end in the thalamus in relation to neurons of the third order, whose axons pass to the cerebral cortex (Fig. 142, p. 637). It is evident from the discussion on p. 596 that some interoceptive impulses also travel in the spinothalamic tracts.

Efferent Systems. Nerve fibers bearing motor impulses from the cerebral cortex descend, without a break, in the corticospinal tracts and end around the motor nerve cells of the ventral gray column. It is probable that an interneuron is interposed between the terminations of the fibers of the pyramidal system and the motor cells of the ventral column. These motoneurons are the final common paths to the skeletal muscles.

Nerve fibers from reflex centers of the brain-stem (acoustic, optic, vestibular) descend in such tracts as the tectospinal and vestibulospinal to end around the motor nerve cells of the ventral column. They convey to the motoneurons impulses concerned in acoustic, optic, and vestibular reflexes.

Efferent paths from the cerebellum convey to the motoneurons impulses concerned in the delicate adjustment of the complex movements caused by the contraction of skeletal muscle. Three neurons are present in this path. The first is a Purkinje cell of the cerebellar cortex from which an axon runs to the dentate nucleus of the cerebellum, where it ends in synaptic relation with a second neuron. This second neuron sends a fiber to end around a nerve cell of the red nucleus, from which a third axon passes, in the rubrospinal tract, to the motoneurons of the spinal cord.

Nerve impulses from the corpus striatum and premotor area reach the motoneurons via the rubrospinal tract.

Efferent pathways are shown in Figs. 139 and 141 (pp. 619 and 636).

Chapter XXXII

THE BRAIN-STEM AND CEREBELLUM

THE brain-stem includes approximately the same parts of the brain as the segmental apparatus, which is so called because it still shows to some extent the segmental arrangement characteristic of the primitive neuraxis. This arrangement is well preserved in the spinal cord. The cerebellum and cerebral hemispheres, being more recent acquisitions by the organism, are sometimes spoken of as suprasegmantal apparatus. The principal structures entering into the formation of the brain-stem are the medulla oblongata, pons, midbrain, interbrain, and basal ganglia.

The midbrain, interbrain, and basal ganglia are parts of the cerebrum, but for convenience the significance of the midbrain and interbrain will be considered here. The basal ganglia will be discussed in a subsequent chapter.

THE MEDULLA OBLONGATA, PONS, AND MIDBRAIN

The functions of the *medulla oblongata* may be stated in terms of its content of white and gray matter. (1) It contains the fiber tracts connecting the higher parts of the brain and the spinal cord; and (2) it contains the primary sensory and motor nuclei, or centers, of several of the cranial nerves and the correlation neurons between these sensory and motor centers, which arrangement enables a great number of reflexes to take place.

The *pons* is made up of a dorsal or tegmental part and a ventral or basilar part. The dorsal part resembles the medulla oblongata anatomically and physiologically, and may be regarded as its forward continuation. The ventral part of the pons contains the fibers of the corticospinal tract, fibers from the cerebrum to the nuclei of the pons, and fibers from these to the cerebellum. The course and function of the corticospinal tract are discussed elsewhere. The other fibers just mentioned constitute a corticopontocerebellar path. The corticopontile fibers originate from cells of the cerebral cortex and terminate around the cells of the nuclei of the pons. The latter cells give origin to pontocerebellar fibers which cross the median plane and penetrate the cerebellum by way of the brachium pontis, or middle cerebellar peduncle.

The *midbrain* or *mesencephalon* consists or two parts: a dorsal part, the corpora quadrigemina or colliculi—four rounded prominences, two anterior and two posterior; and a ventral part, the cerebral peduncles. The anterior pair of colliculi is chiefly a visual reflex center; the posterior pair, chiefly an auditory reflex center. Cross-sections show that each cerebral peduncle is made up of three parts, which, from above downward, are the tegmentum, the substantia nigra, and the basis pedunculi. The tegmentum may be regarded, structurally and functionally, as a forward continuation of the dorsal part of the pons. It contains the red nucleus and the nuclei of the trochlear and oculomotor nerves. The substantia nigra is composed chiefly of deeply pigmented nerve cells of unknown functional significance. The basis pedunculi consists of descending fibers including the corticospinal, corticobulbar, and corticopontile tracts.

Many of the foregoing facts, and others, with respect to the medulla, pons, and midbrain are illustrated in Figs. 139 and 141.

Summary of Functions. The medulla oblongata, pons, and midbrain contain numerous ascending and descending pathways; the sensory and motor nuclei of all the cranial nerves except the first two, together with the interneurons between these nuclei; and a large part of the central mechanism of the postural reflexes (Chapter XXXIII). In the brain-stem are found also several reflex centers concerned in the regulation of important visceral functions such as heart rate, vasomotor tone, and motor and secretory activities of the alimentary canal. A respiratory center is also present. Reference has been made to these centers in appropriate places. The exact locations and the boundaries of the centers are not well known.

Cranial Nerves. All the cranial nerves except the first two—olfactory and optic—are connected with the medulla oblongata, pons, or midbrain. The spinal nerves are arranged in a definitely segmental manner, and this was the primitive condition in the cranial nerves, but in the adult mammal their segmental arrangement has been greatly altered on the afferent side so as to allow afferent fibers possessing similiar physiological functions to discharge into a single center of the brain-stem. As regards the motor roots and nuclei, the segmental arrangement is still fairly evident (Herrick). For the arrangement of the cranial nerves, books on anatomy and neurology should be consulted.

THE INTERBRAIN

The interbrain or diencephalon comprises, from below above,, the hypothalamus, thalamus, and epithalamus. The *hypothalamus* contains the hypophysis or pituitary body, the mammillary body, which is paired, and the tuber cinereum. The hypophysis is an endocrine organ. The mammillary body and tuber cinereum constitute what is commonly meant by the hypothalamus in physiological literature. The hypothalamus is largely concerned in the integration of functions carried out through the autonomic nervous system. Located in the posterior part of the hypothalamus is a central mechanism through which the entire sympathetic system can be called into action. It is the central mechanism mediating the emergency function of the sympathetic (p. 661). A heat-regulating center is located in the hypothalamus. There is also evidence that parasympathetic integration is effected by hypothalamic centers, especially in the middle and anterior portions. The centers of the hypothalamus are subject to regulation by the thalamus, corpus striatum, and cerebral cortex.

The *epithalamus* contains the epiphysis or pineal body and the habenula. The epiphysis of higher vertebrates possibly functions as an endocrine organ. The habenula is an olfactory correlation center.

The *thalamus* (Figs. 139, 141, 142), the largest component of the interbrain, consists of a great number of nuclei which may be divided into three main groups (Fulton): (1) Those that relay to the cerebral cortex impulses from the somatic afferent systems and from the paths of special sense, (2) association nuclei, having connections with other regions of the interbrain or with the cerebral cortex, and (3) nuclei with purely subcortical connections.

Impulses concerned with touch, warmth, cold, localization of sensation (especially pain), taste, proprioceptive sensibility, vision, and hearing are poured into the thalamic nuclei, for relay to the cerebral cortex. Thus the spinothalamic tracts (touch and pressure, localization of pain, warmth, cold, etc.) and the medial lemniscus (proprioceptive sensibility) end in the ventral posterior nucleus of the thalamus from which the path is continued to the cortex via the somesthetic radiation. Audition involves the medial geniculate body, and vision the lateral geniculate. All sensory impulses (except olfactory) destined for the cerebral cortex pass through the thalamus, which is therefore a relay station for the great afferent systems. In addition, impulses from the cerebellum to the cerebral cortex concerned with unconscious proprioceptive functions enter the ventral lateral nucleus of the thalamus, from which they are relayed to the cerebral cortex.

The association nuclei of the thalamus send fibers to the cerebral cortex and they make numerous connections with the nuclei that give rise to the somesthetic and other radiations. There is also a corticothalamic system of fibers, the functional significance of which is not clear.

They doubtless enable the cortex to exert some sort of regulatory influence over the thalamic centers.

The significance of the nuclei having purely subcortical connections is not well understood. They are probably concerned with visceral functions and associative actions within the interbrain. When the cerebral cortex is removed these nuclei are not affected by any degenerative process.

The subthalamic portion of the thalamus is believed to be a motor co-ordination center.

Many workers have emphasized the close functional relationship between the thalamus and the cerebral cortex. Head and Holmes believed that in man certain of the thalamic nuclei are the terminal centers of nerve impulses that arouse conscious reactions of the affective or emotional type—reactions concerned with pleasure and discomfort. These are the more primitive sensations, which lack discriminative qualities. The cerebral cortex receives those sensations requiring discrimination.

THE CEREBELLUM

Anatomical. The cerebellum is a part of the suprasegmental apparatus. It is an outgrowth of the medulla, especially the vestibular nuclei. The cerebellum consists of two fundamental parts: a *flocculonodular lobe,* or vestibular portion, and the *corpus cerebelli*, or spinocortical portion. The flocculonodular lobe sends fibers to and receives fibers from the vestibular nuclei. It is concerned with equilibrium. Because it is phylogenetically the most ancient part of the cerebellum, it is sometimes referred to as the archicerebellum. The corpus cerebelli consists of a phylogenetically old portion, the paleocerebellum, concerned with postural adjustments and tonus, and a neocerebellar portion, which co-ordinates volitional movements.

Sections through the cerebellum show that it consists of a white core covered with a cortex of gray matter. The white core is composed in the main of fibers that enter and leave the cerebellum by way of the three pairs of peduncles, which attach the organ to the underlying brain-stem. Located in the white matter are the several cerebellar nuclei. The cerebellar cortex is composed in large part of nerve cells.

The cerebellar peduncles are (1) the posterior peduncle or restiform body, (2) the middle peduncle or brachium pontis, and (3) the anterior peduncle or brachium conjunctivum. These peduncles contain the fiber tracts leading to and from the cerebellum. The tracts of the posterior and middle peduncles are principally afferent; those of the anterior peduncle are, with the exception of the ventral spinocerebellar tract, efferent.

The cerebellum in relation to the subcortical motor system is shown in Fig. 139 and in relation to the cortical motor system in Fig. 141.

Cerebellar Functions. In an effort to solve the problem of cerebellar function, investigations have proceeded along three main lines: morphological, experimental, and clinical. A few of the morphological aspects of the organ have just been given. Experimental inquiry has involved the use of two main methods, namely, extirpation and electrical stimulation. Careful studies of clinical cases have often yielded illuminating results.

The cerebellum may be said to comprise three organs, each with its own function. (1) The flocculonodular lobe through its connections with the vestibular nuclei helps in the control of equilibrium. (2) The paleocerebellum, receiving impulses from the spinal cord and the vestibular nuclei, is concerned in the integration and inhibition of the postural reflexes. (3) The neocerebellum is an organ for the reception of impulses from the entire proprioceptive field, including the vestibular receptors, and for the discharge of motor impulses whose function is to co-ordinate or synergize the complex movements occasioned by the activity of skeletal muscles. This function of co-ordination is probably carried out by close co-operation of the cerebellum with the cerebral motor cortex rather than by direct participation of the cerebellum in the reflexes of the brain-stem and spinal cord. This function is more important in primates than in lower mammals.

Experimental Removal. The cerebellum has been removed experimentally in animals from amphibians to mammals. Extensive studies have been made in pigeons. The decerebellate pigeon is at first unable to walk or fly. When walking is attempted convulsions occur. After a while the condition improves, and the bird learns to walk, but not normally; ability to fly is again acquired, and the maintenance of equilibrium becomes good; the capacity to take food returns. However, complete recovery from cerebellar removal does not take place. Consciousness and sensory phenomena are unaffected, even from the first; the symptoms are entirely of motor origin. Cerebellar extirpation in the rooster has been found to produce symptoms similiar to those just described.

Luciani was the first to make extensive studies of the effect of cerebellar removal in mammals. The animals used in his studies were dogs and monkeys. Luciani divided the symptoms of cerebellar removal into three groups, which, in the order of their appearance, comprised

(1) the phenomena of functional exaltation, or the dynamic phenomena, (2) the phenomena of deficiency, and (3) the phenomena of compensation.

During the period of functional exaltation there is agitation, unrest, opisthotonos, tonic extensor spasms of the front limbs, alternating clonic spasms of the hind limbs, and staggering. The symptoms resemble somewhat those observed in decerebrate rigidity—a condition of greatly augmented tonus of the extensor muscles and lack of tonus of the flexor muscles seen in animals whose brain-stem is severed in the region of the midbrain—and are caused in part by a loss of the inhibitory influence of the cerebellum over this antigravity reflex. The power of locomotion, greatly interfered with, is gradually restored, although imperfectly. The symptoms of functional exaltation subside in 5 to 10 days and the deficiency symptoms supervene.

Luciani divided the deficiency symptoms into three groups: asthenia or muscular weakness; atonia or diminution of muscular tonus; and astasia—a term including tremor, rhythmic oscillating movements, and titubation or reeling.

Compensatory phenomena make their appearance during the second phase. For the most part functional in character, compensation consists chiefly in abduction of the limbs in walking, so that the base of support of the body is widened and the center of gravity lowered. Thus the animal is less likely to fall. Functional compensation is believed to be due to the assumption of increased control over the muscles by the cerebrum.

Since each half of the cerebellum exerts its influence over the corresponding half of the body, ablation of half of the organ produces symptoms on the operated side similiar to those produced when the whole organ is removed.

The effects of partial decerebellation depend on the region removed. Isolated lesions give different responses that depend on the location of the lesion. Damage to the flocculonodular lobe, for example, results in severe disorders of equilibrium.

It is generally recognized in mammals, as in lower vertebrates, that removal of the cerebellum produces no disturbance of consciousness and sensation.

Partial agenesis of the cerebellum is sometimes seen in animals. Permanent symptoms of cerebellar deficiency are evident in such cases.

Electrical Stimulation. Many workers have resorted to electrical stimulation of the exposed cerebellar cortex in the hope of throwing light on cerebellar function. Contraction or relaxation of skeletal muscle is the reaction usually looked for. Although the literature contains numerous reports of conflicting results, the work of Miller and Banting, in which particular care was taken to prevent spread of the stimulating current to the cerebellar nuclei, supports the view that the cerebellar cortex is electrically excitable, at least in certain regions. In cats showing decerebrate rigidity, inhibition, and occasionally contraction, of skeletal muscle could be obtained by stimulation of different parts of the cerebellar cortex. More recent work indicates that it is the paleocerebellum that shows the greatest response to electrical stimulation.

Chapter XXXIII

POSTURAL REFLEXES

MUSCLE TONUS

MUSCLE tonus or tone is that state of muscle tension which enables an animal to assume and remain in the erect attitude. Sherrington says, "The reflex tonus is postural contraction. . . . The reflex tonus is in short reflex posture." Tonus, or postural contraction, of skeletal muscle is basically a proprioceptive reflex with much of its central control resident in the brain-stem.

Experiments show that tonus occurs chiefly in those muscles concerned in maintaining the animal in an erect attitude. Naturally, therefore, one would expect to find a high degree of tonus in the muscles that counteract the force of gravity—the antigravity muscles. In the standing attitude it is marked in the extensor muscles of the limbs. It is also distinctly present in the muscles that bend the back upward, lift the head and neck, keep the jaws closed and the eyes open, and raise the tail. It is probably present in the ventral muscles of the abdominal wall. The antagonists of these antigravity muscles possess less tonus. If the attitude of the animal changes, muscle tonus must also change.

Although smooth muscle possesses the inherent property of tonus, this is not true of skeletal muscle. Tonus in skeletal muscle is caused by nerve impulses reaching the muscle from the central nervous system. This is shown by the fact that severing the motor nerve of a muscle causes it to lose its tonus and become flaccid. Moreover, skeletal muscle tonus is a *reflex* manifestation, the afferent stimuli originating to a considerable extent in the muscles themselves. This is indicated by the decrease or disappearance of tonus in a muscle when its afferent nerves are cut.

Decerebrate Rigidity. The tonus of skeletal muscles can be studied in the mammalian preparation showing decerebrate rigidity. When the brain-stem is transected between the anterior colliculi and the vestibular nuclei decerebrate rigidity develops. The animal exhibiting this condition is usually designated as a decerebrate animal, sometimes as a bulbospinal animal.

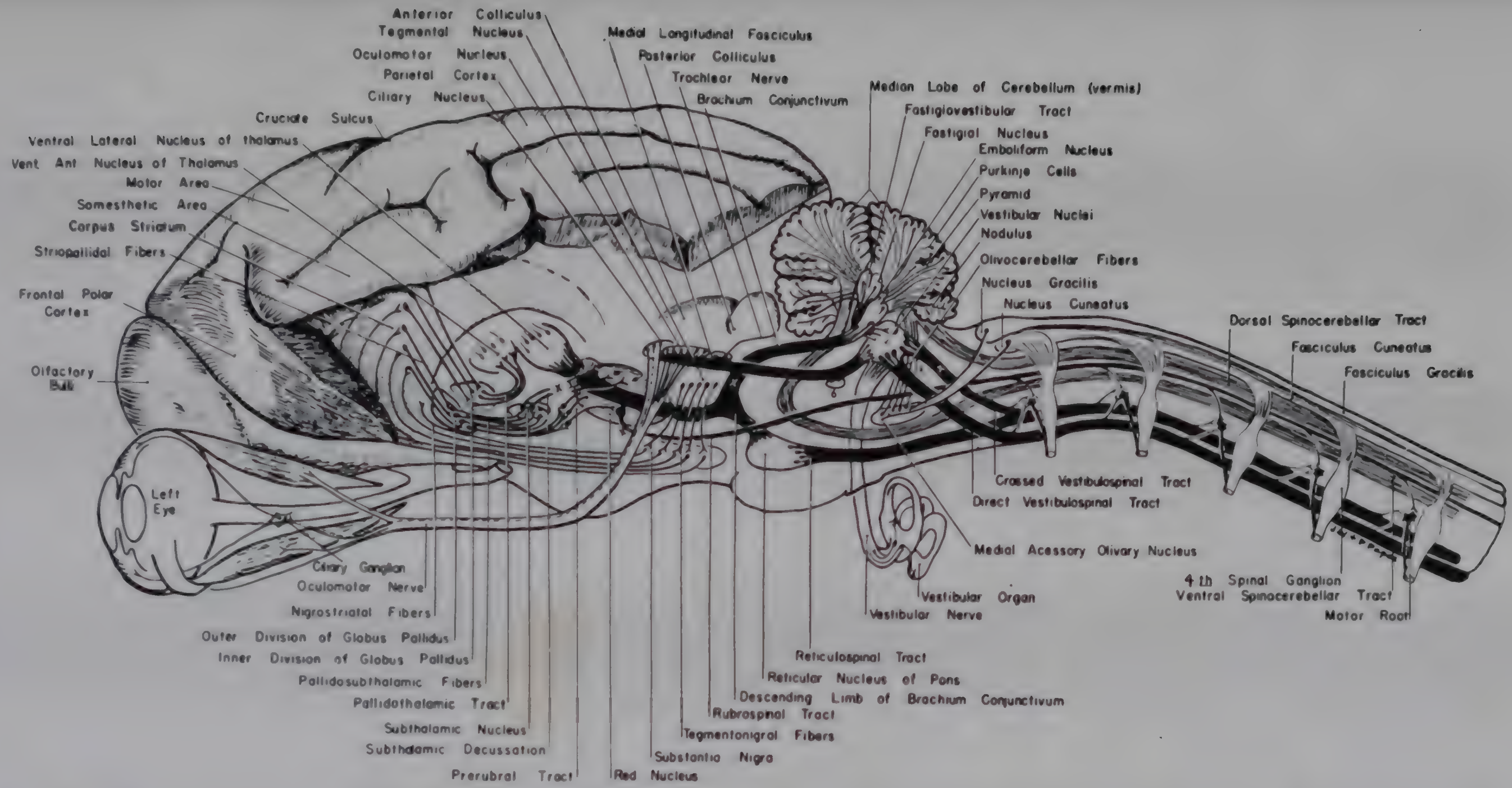
Decerebrate rigidity is characterized by strong tonic contraction of the extensor muscles of the limbs and other muscles concerned in maintaining the animal in the erect attitude, and by only slight tonus of their antagonists. That the muscular contraction in decerebrate rigidity is due to the influence of the nervous system may be shown by cutting the nerve to the muscle in question, whereupon relaxation occurs. The reflex nature of the hypertonus may be shown by section of the dorsal roots of the nerves supplying the muscle. This results in a decrease, or in some locations a disappearance, of the rigidity. Decerebrate rigidity is exaggerated reflex standing; it is a caricature of normal standing.

In the dog and cat the rigidity is evident almost immediately, or within a few minutes, after the transection of the brain-stem, but additional time is usually required for it to reach its greatest intensity. If a survival preparation is made, the rigidity may persist for an indefinite time.

Decerebrate rigidity has been produced in animals of many species and the general picture is much the same in the different animals. Dukes, Danks, Jensen, and Lanfair (unpublished) produced decerebrate rigidity in a young horse by transection of the brain-stem at the usual level. The rigidity that followed was very intense. The horse could stand if given sufficient support to balance itself. The destruction of a small segment of the brain-stem posterior to the level of transection (region of the colliculi) caused the rigidity to disappear. The anesthetic was nembutal and a chloroform-ether mixture.

Decerebrate rigidity is a *release* phenomenon. This means that nerve centers in the brain-stem which are normally held in check, or inhibited, from higher levels of the nervous system become overactive when the inhibitory pathways are transected. Experimental work tends to show that the lateral vestibular nucleus is the chief reflex center of decerebrate rigidity. When this nucleus is freed from inhibitory control by section of the brain-stem in the region of the midbrain, it becomes excessively active in transmitting impulses, via the vestibulospinal tracts, to the motoneurons of the antigravity muscles, and the intense contractions that characterize decerebrate rigidity result (Fig. 139).

Sources of the Inhibitory Effect. The inhibitory influence that keeps the vestibular nuclei under control is not transmitted by the pyramidal pathway; it is an extrapyramidal effect. This was indicated even in the early work, near the turn of the century, on decerebrate rigidity. Later experiments tended to show that the red nucleus is the inhibitory center, but more recent work has demonstrated that higher levels of the nervous system, including the interbrain, basal ganglia,



Anterior Colliculus
Tegmental Nucleus
Oculomotor Nucleus
Parietal Cortex
Ciliary Nucleus
Cruciate Sulcus
Ventral Lateral Nucleus of thalamus
Vent Ant Nucleus of Thalamus
Motor Area
Somesthetic Area
Corpus Striatum
Striopallidal Fibers
Frontal Polar Cortex
Olfactory Bulb
Left Eye
Ciliary Ganglion
Oculomotor Nerve
Nigrostriatal Fibers
Outer Division of Globus Pallidus
Inner Division of Globus Pallidus
Pallidosubthalamic Fibers
Pallidothalamic Tract
Subthalamic Nucleus
Subthalamic Decussation
Prerubral Tract
Red Nucleus
Substantia Nigra
Tegmentonigral Fibers
Rubrospinal Tract
Descending Limb of Brachium Conjunctivum
Reticular Nucleus of Pons
Reticulospinal Tract
Medial Longitudinal Fasciculus
Posterior Colliculus
Trochlear Nerve
Brachium Conjunctivum
Median Lobe of Cerebellum (vermis)
Fastigiovestibular Tract
Fastigial Nucleus
Emboliform Nucleus
Purkinje Cells
Pyramid
Vestibular Nuclei
Nodulus
Olivocerebellar Fibers
Nucleus Gracilis
Nucleus Cuneatus
Dorsal Spinocerebellar Tract
Fasciculus Cuneatus
Fasciculus Gracilis
Crossed Vestibulospinal Tract
Direct Vestibulospinal Tract
Medial Acessory Olivary Nucleus
Vestibular Organ
Vestibular Nerve
4 th Spinal Ganglion
Ventral Spinocerebellar Tract
Motor Root

FIG. 139.—Diagram of the subcortical motor system of the dog showing the connections of the vestibular system, median lobe of the cerebellum, reticular nucleus of the pons, and red nucleus. The subcortical connections of the substantia nigra, corpus striatum, the two divisions of the globus pallidus, subthalamic nucleus, and red nucleus are also shown. The area designated as tegmental nucleus of the midbrain receives many afferent fibers whose exact source is not known. Therefore our knowledge of subcortical innervation of the substantia nigra is uncertain. The oculomotor and ciliary nuclei, in the region of the anterior colliculus, are included, and their innervation of some of the eye muscles and the ciliary muscle is shown. *6* is the nucleus of the abducens nerve. An × indicates decussation of a tract. The vestibular organ is drawn in a ventral position for diagrammatic reasons. (Designed and drawn by Dr. James W. Papez, Cornell University.)

and cerebral cortex, are concerned. The evidence is derived from transections of the brain-stem above the vestibular nuclei and from decortication experiments. Part of the inhibitory effect arises in the paleocerebellum (p. 613). If this portion of the cerebellum is destroyed in a decerebrate animal, the rigidity becomes more intense.

The Mechanism of Muscle Tonus. That the tonus of skeletal muscles is maintained by impulses reaching the muscles from the central nervous system is generally recognized. It is also known that the muscular contractions underlying tonus are accomplished with a low expenditure of energy and with only slight manifestations of fatigue, whereas the muscular contractions that produce movement (phasic contractions) are readily fatigable. These facts suggest that there may be fundamental differences between the two kinds of contractions with respect to the nervous and muscular mechanisms involved.

The idea has been held that the sympathetic nervous system is necessary for sustained contraction, but this view is not supported by recent work (Fulton). Complete removal of the sympathetic nervous system affects the postural responses only slightly.

Antigravity muscles are made up of two kinds of fibers: slowly contracting red ones and rapidly contracting white ones. The theory that the slowly contracting red fibers are the tonus fibers and the rapidly contracting white fibers the ones that cause the quicker phasic contractions is now well supported (Fulton). The frequency of the nerve impulses in the motoneurons supplying the red fibers is low, only about 5 to 10 per second. This fact helps to account for the low fatigability of the muscle fibers concerned in tonus and the slight expenditure of energy that accompanies tonic contraction.

The physiological flexor muscles do not contain red (tonus) fibers; they are made up only of the pale (rapid) muscle fibers.

Sources of Afferent Stimuli. Much evidence favors the view that muscle tonus is fundamentally a proprioceptive reflex, the afferent stimuli arising to a considerable extent in the muscles themselves and reaching the central nervous system by way of the dorsal root fibers. The muscle, particularly its fleshy portion, contains receptors (muscle spindles) which are stimulated mechanically when the muscle is stretched, as when the body tends to fall under the pull of gravity. This stretches extensor muscles, thus stimulating their proprioceptors and evoking reflex contraction. This reflex, known as the *stretch* or *myotatic reflex*, has been studied by Liddell and Sherrington. These workers found that, within limits, reflex contraction of the muscle continues to increase as long as the stretch is increased. When the stretch is discontinued, the reflex contraction ceases immediately. There is therefore little or no after-discharge. The receptors for the stretch reflex show only slow adaptation. The advantage of this fact in the normal working of the antigravity mechanism is obvious. The stretch reflex of those muscles that maintain the animal in the erect attitude is regarded as the fundamental element of which tonus is built.

Other receptors are concerned in the activity of the tonus and other postural reflexes in the normal animal. Some of these receptors are (1) proprioceptors in the vestibular organ (p. 625), especially for the front limbs; (2) exteroceptors, chiefly those of pressure, in the surface of the body; (3) exteroceptors for distance stimuli (teleceptors) in the eye and ear.

OTHER POSTURAL REFLEXES

The postural reflexes have been extensively studied in many animals, especially by Magnus and his collaborators. A detailed discussion of these reflexes will not be entered into here. Other sources may be consulted for a fuller account (Fulton). Following are the postural reflexes that will be considered here: standing reflex; static reflexes, comprising attitudinal and righting reflexes; statokinetic reflexes; placing reactions or reflexes; and hopping reactions.

The Standing Reflex. This is manifested in an exaggerated form in decerebrate rigidity. In the latter condition the tonus of the extensor muscles is excessive, whereas that of the flexors is reduced. In normal standing the flexor muscles, as well as the extensors, show tonus, which, however, is more marked in the antigravity group. By means of this tonic contraction the joints become fixed and the limbs converted into rigid pillars. This is spoken of as the *positive supporting reaction.* It is in part an exteroceptive reflex, evoked by contact of the foot with the ground, and in part a proprioceptive reflex, evoked by the stretch of muscles. The change from this condition to the toneless limb with moveable joints is designated as the *negative supporting reaction.* To attain this condition the strong tonus that characterizes the positive supporting reaction must be inhibited by means of proprioceptive reflexes.

Attitudinal Reflexes. By means of these reflexes displacement of one part of the body is followed by postural changes in other parts, so that a new attitude is struck. These reflexes can be studied in the decerebrate preparation. They may be divided into (1) segmental reflexes, in which only one segment of the body is concerned, and (2) general reflexes, by which the whole body may be affected.

An example of a segmental attitudinal reflex is seen when a decerebrate preparation is set on its feet and a hind foot is pinched. A homolateral flexion reflex is set up and the stimulated limb is withdrawn from the ground; but the body of the animal does not sink to the ground, for an attitudinal (extensor) reflex is evoked in the opposite limb by which the member is enabled to support its increased load.

General attitudinal reflexes are most readily elicited by altering the position of the head. In this way the body may be made to strike many attitudes that resemble those seen in the normal animal. Magnus divides these reflexes into two groups: (1) tonic labyrinthine (vestibular) reflexes acting on the body, and (2) tonic neck reflexes acting on the body. The former are inaugurated by the proprioceptors in the vestibular organ; the latter, by the proprioceptors in the neck muscles and related structures. If it is desired to study the vestibular reflexes alone, the neck reflexes must be excluded, and this can be done by dorsal-root section or by placing the neck in a cast. On the other hand, if it is desired to study the neck reflexes alone, the vestibular organ must be destroyed. When both types of reflex are present, the resulting attitudinal responses are very complicated. Magnus points out the normal uses of these attitudinal reflexes but emphasizes that in the intact monkey and in man, because of the great development of the cerebral cortex, the reflexes are difficult to detect. They are not difficult to detect in other intact animals. A cat looking up at a cupboard shows a very different distribution of tonus in the muscles of the front legs than when looking under a couch. Vestibular and neck reflexes induced by changes in the position of the head determine the conditions of tonus in the limb muscles.

Righting Reflexes. If a decerebrate animal is pushed over, it cannot return to the standing posture; it possesses no power of righting itself. If, however, a midbrain animal—an animal in which the forebrain is removed but the midbrain is left intact—is examined, it will be seen to possess full power to return reflexly from abnormal positions to normal ones. Its righting reflexes function normally. In preparing the midbrain animal the interbrain may be left intact, whereupon temperature regulation is maintained. Such a preparation could be termed an interbrain animal. It is approximately the same as the decorticate animal, which is considered elsewhere (p. 632).

The righting reflexes are divided by Magnus into five groups, as follows: (1) labyrinthine (vestibular) righting reflexes, arising from the otoliths and acting on the head; (2) body righting reflexes acting on the head, the stimuli arising from the exteroceptors of the body surface because of pressure; (3) neck righting reflexes, proprioceptive, acting on the body; (4) body righting reflexes acting on the body, the stimuli arising from the exteroceptors of the body surface; and (5) in some mammals, with intact cerebrum, optical righting reflexes.

The righting reflexes operate of course in the fully intact animal, but their experimental analysis requires destruction of the vestibular organs, deafferentation of the neck muscles, blindfolding, equalization of pressure on the body surface, and other procedures. A well-known example of a righting reflex is the one that occurs when a cat is dropped in the back-down position. The animal goes through a series of movements by which it turns itself in the air so as to land on its feet. It is not an optical righting reflex, as it occurs when the animal is blindfolded. It is a labyrinthine righting reflex, for a blindfolded cat with destroyed vestibular organs fails to right itself and lands on its back.

Kleitman and Koppányi have studied the righting reflexes in the fowl and duck.

Statokinetic Reflexes. These reflexes are evoked when the body is suddenly subjected to angular or linear accelerations, positive or negative. The receptors are located in the semicircular canals (p. 625). A good example of a statokinetic reflex is seen when a blindfolded or decorticate bird is suddenly moved downward and forward in space. The toes fan out in preparation for lighting. It is a vestibular placing reflex. A similar reflex can be elicited by suddenly lowering a blindfolded cat through space. The forelegs become extended and the toes spread out in preparation for landing. (By blindfolding the animal, visual placing reactions are excluded.)

Placing Reactions. Since these responses involve the cerebral cortex, they are more properly called reactions than reflexes. It is essential for normal standing and locomotion that the feet be placed in a position appropriate to the execution of these actions. Two kinds of placing reactions have been described, visual and nonvisual. When a normal animal is lowered toward a table or other surface, visual stimuli cause the forelegs to be placed on the surface in such a way that the legs are at once ready to support the body in standing. If the animal is blindfolded, other stimuli of an exteroceptive and proprioceptive nature enable accurate placing to be accomplished. Bard (1937-38, 1941) has described five nonvisual placing reactions.

1. If a blindfolded cat (or a cat whose head is held up in such a way that it cannot see its front feet or objects in front or below) is supported in the hands and moved toward a table, contact of any portion of the front or hind feet with the edge of the table will result in accurate placing of the stimulated pair on the table close to the edge. This is contact placing. If a single foot is stimulated by the contact,

placing of the opposite foot usually follows as well. This is crossed placing. If the animal can see, visual placing will result.

2. If a blindfolded cat is held suspended in the air and the chin is brought into contact with the edge of a table, the front feet are raised and accurately placed on the table alongside of the jaws. Extension of the limbs and standing usually follow. If a nonblinded animal is used, it is necessary to hold the front feet down; otherwise visual placing will take place. Once the chin is in contact with the table and the legs are released, accurate placing results. This response to chin stimulation may be designated as chin placing.

3. If an animal (blindfolded or not) is allowed to sit, stand, or crouch on a table and the front or hind legs are pushed over the edge, they will be immediately lifted and returned to their original position. This has been termed positional placing.

4. If any leg of a standing animal is passively abducted without being held, it will be returned to its standing position.

5. If a blindfolded cat is held free in the air and moved toward some object until the tips of the vibrissae on one or both sides touch the object, both front feet are accurately placed on it. Unless vision is excluded, a visual placing reaction of the forelegs will result.

Hopping Reactions. If an animal is so held that it stands on one leg and the body is moved forward, backward, or to either side, a corrective hopping movement of the leg takes place in the direction of the displacement. The foot is thus kept under the shoulder or hip and the leg again exhibits the positive supporting reaction by means of which it can act as a rigid pillar. With the leg in the normal standing position, the positive supporting reaction is well defined, but as the leg deviates from this position with displacement of the body the tone of the muscles diminishes, the foot is raised, and the leg is put down in a new normal position where it again acts as a rigid pillar. It is believed that stretch receptors in the muscles initiate the reflex.

CENTRAL MECHANISMS

The nerve centers and the central pathways concerned in the postural reflexes are known in some instances, but in others they are poorly understood or unknown. Most of the centers are above the level of the spinal cord. Thus even in the relatively simple reflex of decerebrate rigidity spinal centers are little concerned. As indicated elsewhere (p. 618), there is evidence to show that the chief reflex center of decerebrate rigidity is the lateral vestibular nucleus, which is situated in the floor of the fourth ventricle. Normal standing can be manifested by the midbrain animal. The centers of the attitudinal reflexes are found behind the plane of entrance of the acoustic nerves. The centers of the righting reflexes, except the optical, have been located in the midbrain. The centers of the neck righting reflexes extend downward as far as the pons and upper part of the medulla oblongata; the centers of the other righting reflexes are found at the level of the red nucleus. In fact, the red nucleus is believed to be the center for the labyrinthine righting reflexes and for the body righting reflexes acting on the body, and their efferent path is the rubrospinal tract. The location of these various centers has been determined mainly by transections of the brain-stem at different levels.

The centers of the optical righting reflexes are located in the cerebral cortex. The placing and hopping reactions are also managed at the cortical level. Bard has determined that the cortical region concerned is a small area situated at the frontal pole of the cortex. It appears to coincide approximately with the motor area of the cortex (p. 635). The control over the muscles is contralateral. The placing and hopping reactions, having to do with the finer adjustments of posture, are managed cortically, whereas most of the other postural responses are managed subcortically.

Whatever the efferent pathways in the postural reflexes may be, it is evident that in the end all efferent stimuli must reach the muscles by way of the motor neurons whose cells of origin are located in the ventral gray column of the spinal cord and similar neurons whose cells of origin are located in the brain-stem, These neurons—motoneurons—constitute the final common paths in the postural reflex circuits.

The work of Magnus led him to conclude that the cerebellum is not concerned in the postural reflexes; that the centers and afferent and efferent paths of the reflexes are extracerebellar. More recent research (Langworthy, Fulton) has not supported this view but has indicated that the cerebellar cortex, or a portion of it, exerts an inhibitory influence over the postural reflexes, particularly the antigravity reflex (p. 613).

VESTIBULAR ORGAN

This structure is such an important receptor in the postural reflex mechanism that its physiology may be studied at this time. The bony labyrinth of the internal ear, lying in the temporal bone, contains the membranous labyrinth. Surrounding the membranous labyrinth and separating it from the bony labyrinth is a liquid known as perilymph. In the cavities of the membranous labyrinth the endolymph is found. The membranous labyrinth is divided into two parts, which differ greatly in their functional significance: (1) the nonacoustic labyrinth or vestibular organ, and (2) the acoustic labyrinth or cochlear duct.

The physiology of the latter is considered in another chapter (p. 681).

The vestibular organ comprises two membranous sacs, known as the saccule and the utricle, and the membranous semicircular canals. The saccule communicates with the cochlear duct and the utricle with the semicircular canals. Connecting the saccule with the utricle is the short ductus utriculosaccularis.

The labyrinth is really the elaborate end-organ of the acoustic nerve. The nerve, as is well known, consists of two parts: the vestibular nerve, supplying the vestibular organ, and the cochlear nerve, supplying the cochlear duct (Fig. 140). The cells of origin of the vestibular nerve fibers are located in the vestibular ganglion. Being bipolar, the cells give off central and peripheral branches. The central branches end in the vestibular nuclei of the brain-stem and in the cerebellum. The peripheral branches end in the maculae of the utricle and saccule and in the ampullary crests of the semicircular canals. The maculae and ampullary crests are located on the inner walls of their respective parts of the vestibular apparatus and contain specialized cells which are the receptors of the vestibular nerve. The cells are in each case ciliated, the cilia of the cells of the maculae being shorter than those of the ampullary crests. The cilia of the cells of the crests

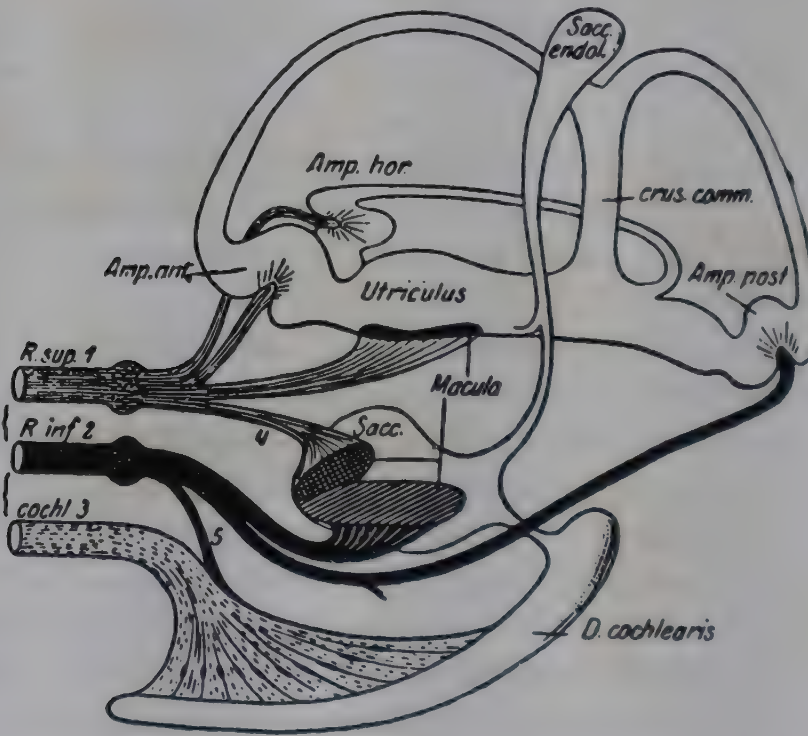


FIG. 140.—Diagrammatic representation of the innervation of the membranous labyrinth. R. sup. 1, R. inf. 2, the vestibular nerve; cochl. 3, the cochlear nerve. (de Burlet; from Camis' *The Physiology of the Vestibular Apparatus*, translated by Creed, The Clarendon Press, Oxford, Eng.)

project into the ampullary cavity of a semicircular canal, but the cilia are not naked; they are imbedded in a gelatinous mass known as the cupola. The cilia of the cells of the maculae, instead of being imbedded in a gelatinous mass, are attached to a mass composed of tiny crystals of calcium carbonate held together by a cement substance. The term otolith is applied to this mass, which forms a sort of membrane over the ciliated cells of the maculae. The position of the macula utriculi when the head is in the normal position is practically horizontal, whereas the position of the macula sacculi is vertical. The semicircular canals, at least their middle portions, lie in the three planes of space.

A question which has long engaged the interest of physiologists relates to the manner in which the receptors found in the ampullary crests and the maculae are stimulated. A completely satisfactory answer is not yet available. Although the functions of the sensory nerve endings in the maculae and crests are not identical, it is nevertheless probable that the distinction between their functions is not sharp. The two parts of the vestibular organ, containing respectively the maculae and crests, apparently reinforce each other. The otoliths react chiefly to changes in position. They produce the greatest stimulus when they hang from and thus pull upon the ciliated cells to which they are attached, and the least stimulus when they press upon the ciliated cells. The otoliths are, according to this view, static organs. There is some evidence that the otolith of the saccule is concerned with sound perception. The ampullary crests of the semicircular canals react to angular and linear accelerations, because of movements in the endolymph. The ampullary crests are therefore kinetic organs.

The vestibular sense is not equally developed in all animals. It is most highly developed in birds, less in mammals, and least in fishes. Among mammals it reaches a high degree of development in the rabbit and guinea pig but is less developed in the monkey and man.

It is evident from the foregoing statements that the vestibular organ is a part of the proprioceptive system and is stimulated, not by changes in the external environment, but by changes in the internal environment.

Chapter XXXIV

THE CEREBRAL HEMISPHERES

THE cerebrum comprehends the midbrain, interbrain, and cerebral hemispheres. The physiological significance of the midbrain and interbrain is discussed in Chapter XXXII. What remains to be studied, in the present chapter, is the cerebral hemisphere, a large, paired structure making up most of the cerebrum. Each hemisphere is composed of a covering of gray matter, termed the cortex or pallium; a central mass of white matter; and the basal ganglia—masses of gray matter, of which the corpus striatum is the most prominent. Since the white matter of the cerebral hemisphere is composed of nerve fibers, which do not modify nerve impulses, and since the basal ganglia, although composed largely of nerve cells, are greatly overshadowed by the cortex, the discussions in this chapter must relate mainly to the cortex.

The cerebral cortex, or pallium, is acquired late in vertebrate evolution and, like the cerebellum, belongs to the suprasegmental apparatus, in contrast with the more primitive segmental apparatus, or brain-stem. The cerebral cortex is concerned with those nervous reactions that result in consciousness. It is the seat of the highest type of nervous correlation, termed association. Whereas the spinal cord and brain-stem mediate the inherent nervous reactions often termed unconditioned reflexes, the cerebral cortex mediates the individually acquired nervous reactions often termed conditioned reflexes. The cortex, especially that of man, is marked by a high degree of educability.

COMPONENT PARTS OF THE CEREBRAL HEMISPHERE

Basal Ganglia. These comprise masses of gray matter located in the white matter of each cerebral hemisphere. They include (1) the corpus striatum, (2) the globus pallidus, (3) the claustrum, and (4) the amygdaloid nucleus. Our knowledge of the physiology of the basal ganglia is still very incomplete.

The corpus striatum consists of two masses of gray matter known as the caudate nucleus and the putamen. In lowly vertebrates that possess no cerebral cortex, and in reptiles and birds, which possess a small cortex, the corpus striatum is well developed. In these animals it appears to be a motor correlation center of great importance. In mammals the relative importance of the corpus striatum is greatly overshadowed by the extensively developed cerebral cortex. The corpus striatum receives fibers from the frontal portion of the cerebral cortex and sends projections to the globus pallidus, whence they are relayed to the red nucleus, thus bringing the rubrospinal tract under cortical and striatal control (Fig. 141). It also receives fibers from the substantia nigra (Fig. 139).

Chorea and other syndromes accompanied by involuntary movements are frequently associated with lesions of the corpus striatum. Chang has reported on choreiform movements in a dog which showed lesions involving principally the corpus striatum and the cerebral cortex.

The corpus striatum and the globus pallidus are the subject of a review by Rioch.

White Matter. The medullary substance, or white matter, of the cerebral hemisphere is composed of innumerable myelinated nerve fibers situated beneath the cerebral cortex. In this mass of white matter the basal ganglia are found. The nerve fibers entering into the formation of the cerebral medullary substance may be divided into three groups: (1) association fibers, (2) commissural fibers, and (3) projection fibers.

The *association fibers* establish connection between the different parts of the cerebral cortex. Two main classes of these fibers can be recognized: short ones, connecting adjacent convolutions, and long ones, connecting the lobes of the cerebrum. Association fibers are most evident in the brains of primates.

The *commissural fibers* form the connecting links between the two cerebral hemispheres. They comprise the corpus callosum, the anterior commissure, and the hippocampal commissure.

The *projection fibers*, motor and sensory, connect the cerebral cortex with the brain-stem and spinal cord. The motor projection fibers form the corticospinal, corticobulbar, corticopontile (frontopontile, parietopontile), corticorubral, and other tracts. The sensory radiations or projection fibers connect the thalamus with the visual, auditory, and somesthetic areas, and the olfactory center at the base of the olfactory bulb with the olfactory area, of the cerebral cortex. Accompanying the thalamocortical radiations are corticothalamic fibers, which conduct in the opposite direction. The exact significance of these fibers is obscure. There is reason to believe that through them the cerebral cortex exerts a regulatory influence on thalamic activity (Tilney and Riley).

The Structure of the Cerebral Cortex. The cerebral cortex or pallium is divisible into a primitive olfactory portion, the archipallium, and a more recent, nonolfactory portion, the neopallium or neocortex. In the higher mammals the neopallium is much more important than the archipallium. In primates, which depend for their existence so little upon the sense of smell, the archipallium is relatively much smaller than in most other mammals. Among mammals, it is best developed in the lowest forms, especially the marsupials.

The cerebral cortex of some of the small mammals, particularly the more primitive ones, is smooth; whereas that of most mammals, including Ungulata, Carnivora, and primates, shows the presence of convolutions or gyri and fissures or sulci, which are more or less characteristically arranged in each higher mammalian order. In primates the cortex of each hemisphere is divided, somewhat arbitrarily, into frontal, parietal, temporal, and occipital lobes. In man the frontal lobe is exceedingly well developed.

Sections through the cerebral cortex show that it is made up of several layers, parallel with the surface of the gyri and consisting of nerve cells and nerve fibers. Six cortical layers are now recognized by neurologists.

Because of the fact that the different cell and fiber layers in the cerebral cortex are not absolutely uniform as to size, number, and other qualities, many workers have mapped out areas in the cortex of many species, based upon these differences. Studies of this kind, while differing and disagreeing in some respects, make it evident that different parts of the cerebral cortex show characteristic structural features in each species, and that in all higher mammals these features are more or less similar. Furthermore, histologists have attempted to correlate their findings with those of experimental physiology and clinical medicine and thus to assign functions to these histologically determined areas. References to this literature may be found in Campbell's monograph, in Bolton's article, and Fulton's book.

Physiologically the nerve cells of the cortex may be assumed to be of three types: those giving rise to projection fibers, those giving rise to association fibers, short and long, and those giving rise to commissural fibers. The nerve fibers of the cortex consist (1) of dendrites, short axons, and the proximal parts of longer axons, derived from the cells of the cortex, and (2) of the terminal parts of nerve fibers entering the cortex from the underlying medullary substance.

METHODS OF STUDYING CORTICAL FUNCTION

No problem in the entire biological field is more baffling than that of cortical function. Many classes of workers have made contributions looking toward a solution of the problem, and many methods of study have been used. Among the workers may be mentioned the anatomists, histologists, embryologists, physiologists, pathologists, clinicians, and psychologists. Some of the procedures that have been used in studies of cortical function are (1) anatomical studies, particularly in the comparative field; (2) histological studies; (3) myelination studies, which depend upon the fact that the medullated fibers of the cerebral cortex acquire their medullary sheaths at different times—some before birth and some after—and upon the assumption that fibers of similar functional significance mature, that is, gain their medullary sheaths, at approximately the same time; (4) electrical excitation of exposed portions of the cerebral cortex; (5) electroencephalography, or the study of the action potentials of the brain: electrical changes of several kinds signaling the activity of the nerve cells of the cerebral cortex and other brain structures; (6) metabolic and other biochemical studies of the brain; (7) experimental removal of the entire forebrain or of parts of it; (8) studies of clinical cases in which parts of the brain have been injured or destroyed accidentally, or in which there are signs of cerebral disease; (9) postmortem studies of lesions in individuals known to have shown certain evidences of cerebral involvement; and (10) studies of conditioned or acquired reflexes.

THE METABOLISM OF BRAIN

The metabolic rate of the gray matter of the brain is high. There is evidence that it is three or four times higher than the metabolic rate of white matter. For its normal functioning the brain must have a continuous supply of blood. It has been shown in dogs that stasis of the brain circulation for eight minutes or longer causes severe damage of a permanent nature to the brain. The injury includes "loss of function of the cerebral cortex, loss of auditory reflexes, of the ability to stand and walk, of emotional reactions and vocalization, as well as dysfunction suggestive of strial involvement" (Kabat, Dennis, and Baker). Complete recovery of function follows arrest of the brain circulation for six minutes.

The respiratory quotient of brain is approximately 1. This was determined by comparing the oxygen and carbon dioxide contents of arterial blood with those of venous blood coming from the brain. In this way an arteriovenous oxygen difference and an arteriovenous carbon dioxide difference are obtained. From the data the respiratory quotient can be calculated. A respiratory quotient of unity indicates carbohydrate metabolism (p. 445). In vitro studies of brain metabolism agree with in vivo studies in showing that the respiratory quotient of brain is approximately 1.

It has been shown that blood on passing through the brain loses glucose, the loss being about 10 mg. per 100 cc. of blood. This indicates that glucose is an important fuel of brain.

In a study of the metabolism of the perfused brain of the adult dog Handley and co-workers concluded "that approximately 50 per cent of the oxygen supplied to the head region is used by the brain and that the brain accounts for about 8 per cent of the total oxygen consumption of the body at rest."

Since anoxia causes such rapid loss of cerebral functions, the brain evidently derives the bulk of its energy from aerobic sources. However, it has been shown that during a period of partial anoxia the brain of the adult animal (dog, cat) obtains enough energy by the anaerobic cleavage of carbohydrate to lactic acid (glycolysis) to prolong for some time the survival period. Nevertheless the tolerance of the adult to anoxia is much less than that of the newborn (Fazekas and coworkers). The explanation is that the metabolic rate of the brain of the newborn is low and that energy can be derived glycolytically— that is, anaerobically—at a rate sufficient to maintain the integrity of the cerebral mechanisms for some time. Newborn puppies and kittens tolerate on the average an exposure of 24 minutes to an atmosphere of pure nitrogen. Newborn rats survive even longer.

THE EFFECTS OF DECORTICATION, REMOVAL OF THE CEREBRAL HEMISPHERES, OR OF THE FOREBRAIN

The effect of decerebration is considered in another place (p. 617). Decortication and removal of the cerebral hemispheres are similar except that in the second instance the basal ganglia are also removed. Extirpation of the forebrain means the removal of the cerebral hemispheres and the interbrain. Because of the surgical difficulties involved the removals do not always follow sharp anatomical limits. This will be apparent in the following discussions.

In all kinds of fish the brain is poorly developed. Removal of the forebrain in teleosteans causes little or no evident effect. They move, feed, and behave toward their intact associates in an apparently normal manner. Selachians likewise show no motor disturbances when the forebrain is removed. However, feeding is interfered with because the operation involves the removal of the olfactory lobes, which are very important in these animals that locate their food by smell.

Removal of the cerebral hemispheres in Amphibia is attended with no serious loss of function. Frogs behave apparently normally as regards ordinary movements, swimming, hibernation, feeding, and vision.

The tortoise moves more sluggishly and exhibits less initiative after the operation.

Removal of the very rudimentary cerebral cortex of the pigeon disturbs its reflex movements only slightly, but its intelligence, capacity to learn, and individual memory, poorly developed though they are in the intact condition, are much reduced. The bird must be fed and watered and kept in a protected environment. If the basal lobes are injured or destroyed, the reflex activities are impaired. The disturbance becomes worse if the thalamus is involved.

Removal of the cerebral cortex or hemispheres or of the forebrain has been accomplished in a number of mammals. The experiment of Goltz, in which both cortices of a dog were removed and the corpora striati, thalami, and corpora quadrigemina were injured, is a classic in physiology. English summaries of this work are given by Luciani and Schafer. Holmes has reported the results of a histological examination of the nervous system of Goltz's dog. Removal of the nervous tissue was accomplished in three successive operations. The dog lived for more than eighteen months after the last operation and was then killed by bleeding. A few days after the last operation the ability to walk returned, and after a time normal locomotion was possible; however, toward the end of the period weakness developed. The animal walked restlessly most of the day but slept at night. A loud sound would awaken it. Hunger was evident, and the dog would eat, but only when food was brought close to its nose. Digestion was good, but the nutritive condition of the animal was only fair. The sense of touch was impaired though not abolished. Painful stimuli evoked movements, barking, and snapping. There was evidence that the sense of taste remained, but the sense of smell was abolished. The sense of hearing was dulled. Vision was profoundly affected, for obstacles were run into; but complete blindness could not have been present, for strong light caused the animal to close the eyes and turn the head away. The pupillary reflexes remained. The psychic functions were greatly reduced. There was no manifestation of fear, affection, pleasure, except in eating, or sexual interest. Persons or other dogs were not recognized; memory and ability to learn were gone. The dog had been reduced to the condition of an idiot; it was merely an automaton, a reflex machine; its individuality was gone.

It may be noted that Goltz's dog lacked not only the cerebral cortex but also parts of the corpus striatum, interbrain, and midbrain. More recent experiments on the dog have shown that when the latter structures are spared the psychic disturbances are not so profound; the dog retains some ability to learn.

Rabbits have been kept alive for as long as six months after removal of most of the neocortex (Ten Cate and Van Herk). Superficially the animals seemed normal, but attempts to burrow were absent and they showed no objection to getting wet. Ability to see and hear returned soon after the operation, and it was possible to establish conditioned reflexes. Tactile sensations were increased.

Schaltenbrand and Cobb kept a cat alive five months after removal of the neocortex. Its motor activity was varied and was greater than that of the normal cat. It reached and ate food without help.

Monkeys do not live longer than a few weeks following removal of the cerebral hemispheres.

LOCALIZATION OF FUNCTION IN THE CEREBRAL CORTEX

An important question relating to the physiology of the cerebral cortex is: Does the cortex function rather uniformly throughout—much as a gland does, for instance—or is it composed of a number of independently working parts such as one for vision, one for touch, one for the higher associations, and one for voluntary movement? Stated otherwise, does localization of function prevail in the cerebral cortex?

Ideas on cortical localization have gone through an interesting history, but only a brief statement can be given here. The phrenologists, pseudoscientists, taught years ago that there is severe localization of the mental functions in the cortex, which was conceived to be a plurality of independently functioning organs. The pioneer physiologists, on the basis of animal experimentation, took the opposite view, that the cortex functions as a whole. When it was found, in 1870, that electrical stimulation of certain parts of the exposed cortex produces contraction of some of the skeletal muscles, a new era in cortical localization was inaugurated, and for a time there was a tendency to return to the sharp localization which characterized the views of the phrenologists. But the pendulum has started back, and modern opinion is that there is, in a manner, motor and sensory localization in the cortex but not in the sense of rigidly circumscribed centers; as to the higher associations, which form such important elements in the mental life of man, modern work does not support the older view that they show cortical localization. The cortex is not equipotential throughout, neither is it a plurality of delimited organs. The various parts, though mediating different functions, are nevertheless mutually interdependent, so that injury to one part may cause dysfunction of distant parts. On the other hand, a lesion of one part does not abolish the function that is represented in that part but, rather, disturbs it. Hines has reviewed the subject of cerebral localization.

A diagram of the cortical motor system of the dog is shown in Fig. 141. The afferent paths to the thalamus and cerebral cortex and the somesthetic, auditory, and visual areas of the cortex are shown in Fig. 142. These figures should be studied in connection with the discussions of the different areas that follow.

Motor Area. Much evidence is available to show that the cerebral cortex of mammals possesses a bilaterally situated area whose electrical stimulation causes muscular movements on the opposite side of the body. This is the so-called motor area. Its position and size vary considerably in different species in harmony with differences in the configuration and the degree of development of the cortex. In general there is a direct relation between the size of the motor area and the number and complexity of the skeletal muscle movements of which the animal is capable. Thus in primates, especially man, it is large, in Carnivora it is of intermediate size; and in Ungulata, in which only simple, pendulumlike movements of the limbs are possible, it is small. A number of workers have shown, in several species, that the motor area as determined by electrical stimulation of the cortex is broadly coextensive with a histologically differentiated type of cortex containing giant pyramidal cells known as Betz cells. These are the cells of origin of some, but by no means all, of the corticospinal (pyramidal) fibers (p. 596).

As stated above, the position and size of the motor area vary in different species. In anthropoids Leyton and Sherrington have shown by electrical stimulation that it is located principally in the anterior central gyrus (Fig. 143). A number of opportunities have arisen of stimulating the cerebral cortex of man under local anesthesia. The observations show that the so-called area 4 (approximately the same as the precentral gyrus) is the most excitable region and that its stimulation yields the most striking motor responses. However, many other regions of the primate cortex respond to stimulation. In Carnivora histological and experimental studies indicate that the motor area is situated in relation to the cruciate sulcus (Campbell). In the sheep similar studies (Simpson and King, Bagley) show that it is located mainly in the superior frontal convolution. The details of the localization, as determined by Bagley, are shown in Fig. 144. The motor area of the goat brain has been studied by electrical exploration (Clark, Ward, and Dribben). It was found that, with minor exceptions, the area resembles that of the sheep. Goats affected with a congenital myotonia showed little difference in response as compared with normal goats. In the pig experimental evidence is lacking, but the histological studies of Campbell suggest that the motor area is located between the coronal sulcus medially and the presylvian sulcus laterally. Typical giant

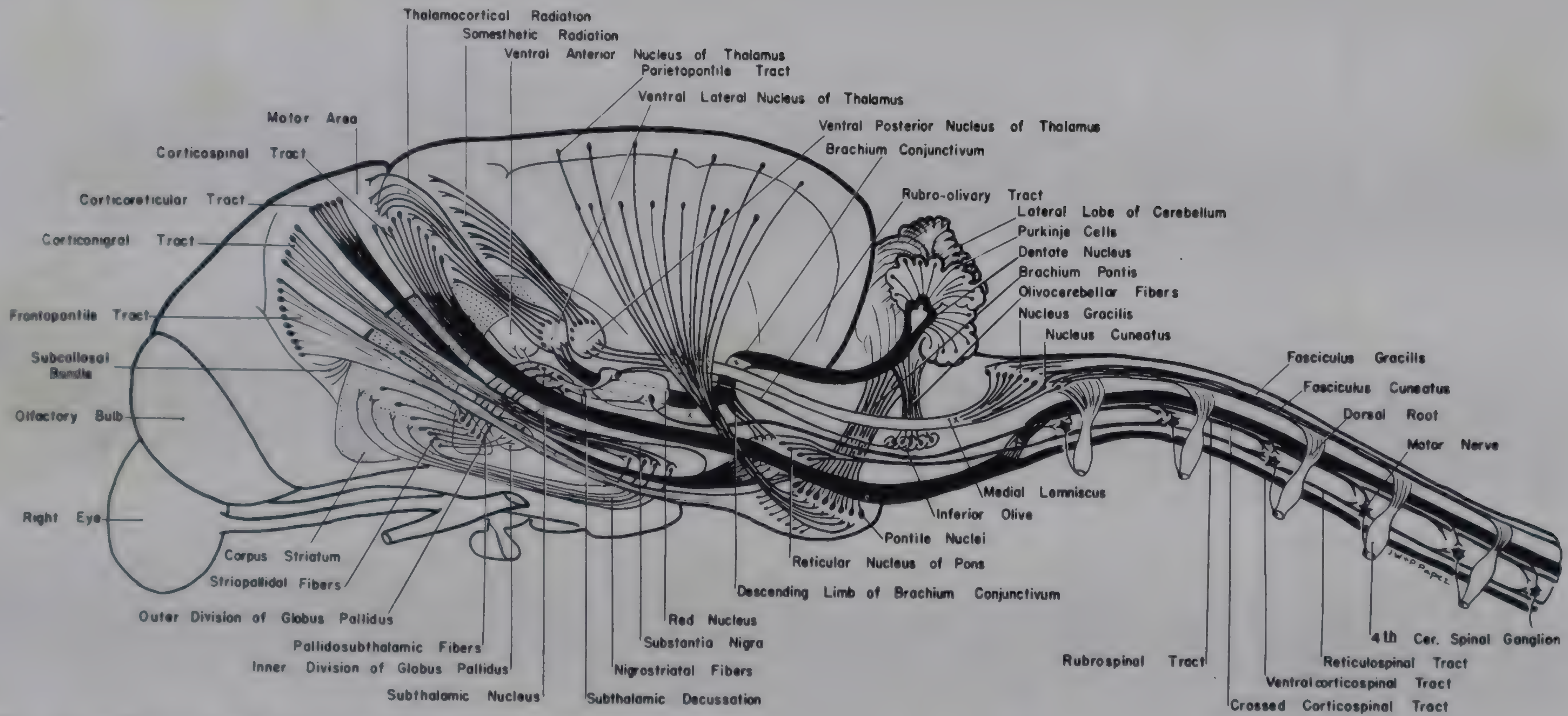

Thalamocortical Radiation
Somesthetic Radiation
Ventral Anterior Nucleus of Thalamus
Parietopontile Tract
Ventral Lateral Nucleus of Thalamus
Motor Area
Ventral Posterior Nucleus of Thalamus
Brachium Conjunctivum
Corticospinal Tract
Corticoreticular Tract
Corticonigral Tract
Rubro-olivary Tract
Lateral Lobe of Cerebellum
Purkinje Cells
Dentate Nucleus
Brachium Pontis
Olivocerebellar Fibers
Nucleus Gracilis
Nucleus Cuneatus
Frontopontile Tract
Subcallosal Bundle
Fasciculus Gracilis
Fasciculus Cuneatus
Dorsal Root
Olfactory Bulb
Motor Nerve
Medial Lemniscus
Inferior Olive
Pontile Nuclei
Right Eye
Reticular Nucleus of Pons
Corpus Striatum
Striopallidal Fibers
Descending Limb of Brachium Conjunctivum
Outer Division of Globus Pallidus
Red Nucleus
Substantia Nigra
Pallidosubthalamic Fibers
Inner Division of Globus Pallidus
Nigrostriatal Fibers
Subthalamic Nucleus
Subthalamic Decussation
4th Cer. Spinal Ganglion
Rubrospinal Tract
Reticulospinal Tract
Ventral corticospinal Tract
Crossed Corticospinal Tract
J. W. Papez

Fig. 141.—Diagram of the cortical motor system of the dog. Represented are the descending paths to the substantia nigra, pontile nuclei, opposite lateral lobe of the cerebellum, and motor neurons of the spinal cord. Descending paths from the corpus striatum, outer division of the globus pallidus, subthalamic nucleus, and red nucleus are shown. Ascending paths from the proprioceptors to the somesthetic area, and from the cerebellum to the cortical motor area, are shown. The ascending path from the substantia nigra to the corpus striatum is also shown. An × indicates that the tract is derived from or crosses to the opposite side. The cortical areas of origin of several of the tracts shown are not known, but by analogy with primate anatomy they have been placed in the region of the sygmoid gyrus. This applies to the corticoreticular, corticonigral, and frontopontile tracts. These three and the parietopontile tract constitute the extrapyramidal system. (Designed and drawn by Dr. James W. Papez, Cornell University.)

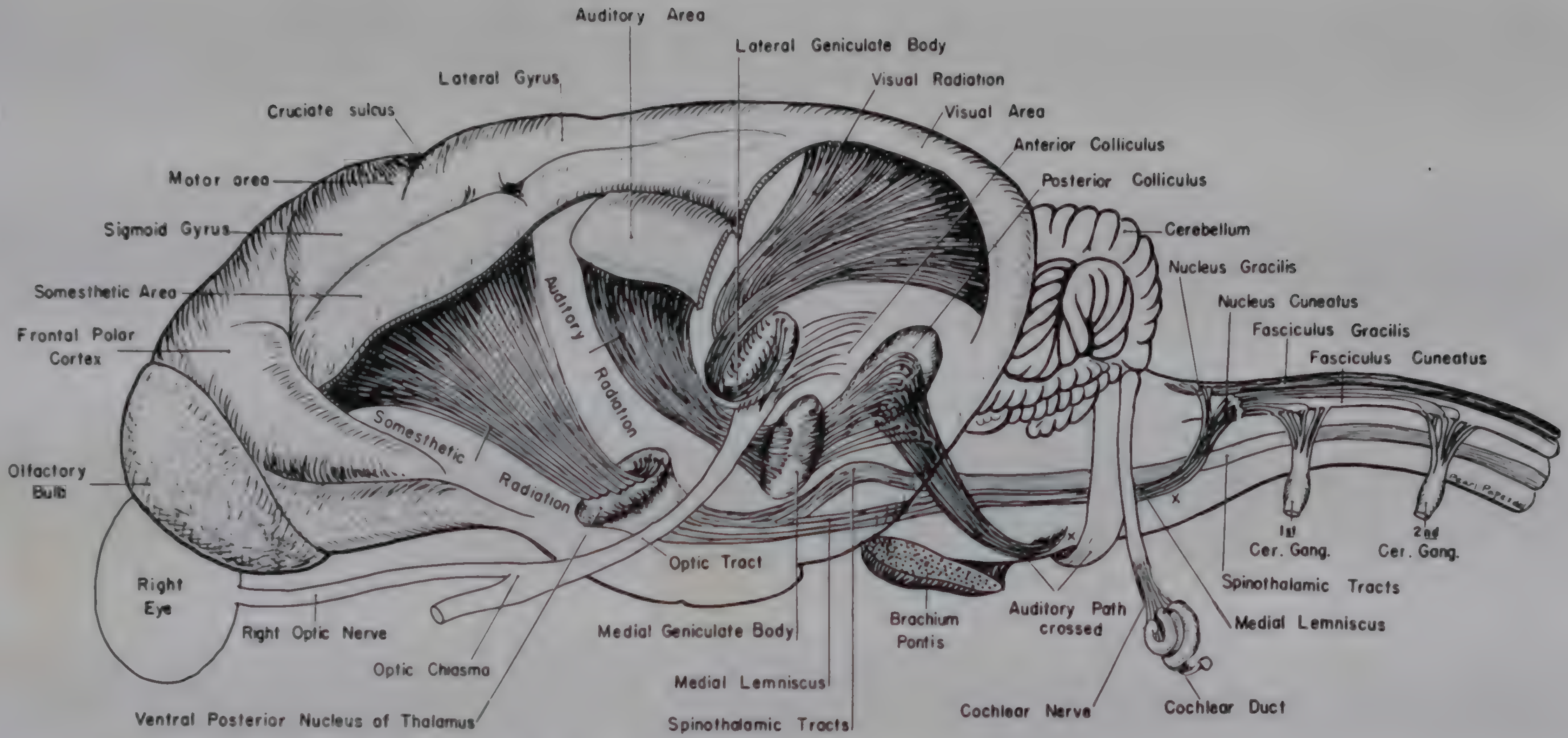

Auditory Area
Lateral Geniculate Body
Lateral Gyrus
Visual Radiation
Cruciate sulcus
Visual Area
Anterior Colliculus
Motor area
Posterior Colliculus
Sigmoid Gyrus
Cerebellum
Nucleus Gracilis
Somesthetic Area
Nucleus Cuneatus
Fasciculus Gracilis
Frontal Polar Cortex
Fasciculus Cuneatus
Auditory Radiation
Somesthetic Radiation
Olfactory Bulb
1st Cer. Gang.
2nd Cer. Gang.
Right Eye
Optic Tract
Spinothalamic Tracts
Right Optic Nerve
Medial Geniculate Body
Brachium Pontis
Auditory Path crossed
Medial Lemniscus
Optic Chiasma
Medial Lemniscus
Cochlear Nerve
Cochlear Duct
Ventral Posterior Nucleus of Thalamus
Spinothalamic Tracts

FIG. 142.—Diagram of the afferent paths to the thalamus and cerebral cortex in the brain of the dog. The four paths represented are cutaneous (and visceral pain), proprioceptive, auditory, and visual. Two cervical segments of the spinal cord are also shown. The thalamic nuclei shown have been separated for clarity of representation and the paths have been simplified for the same purpose. The decussations of the auditory path and the medial lemniscus are indicated by ×. (Designed and drawn by Dr. James W. Papez, Cornell University.)

pyramidal cells are not present. Dukes, Danks, Jensen, and Lanfair (unpublished) stimulated the cerebral cortex of a young horse by means of condenser discharges and unipolar stimulation. Good motor responses were obtained from a bilaterally situated cortical region ("motor area") located just lateral to the lateral limb of the cruciate sulcus. From the middle part of the suprasylvian gyrus (in the lateral parietal region) good responses were also obtained. This region is presumed to be the origin of a parietopontile tract.

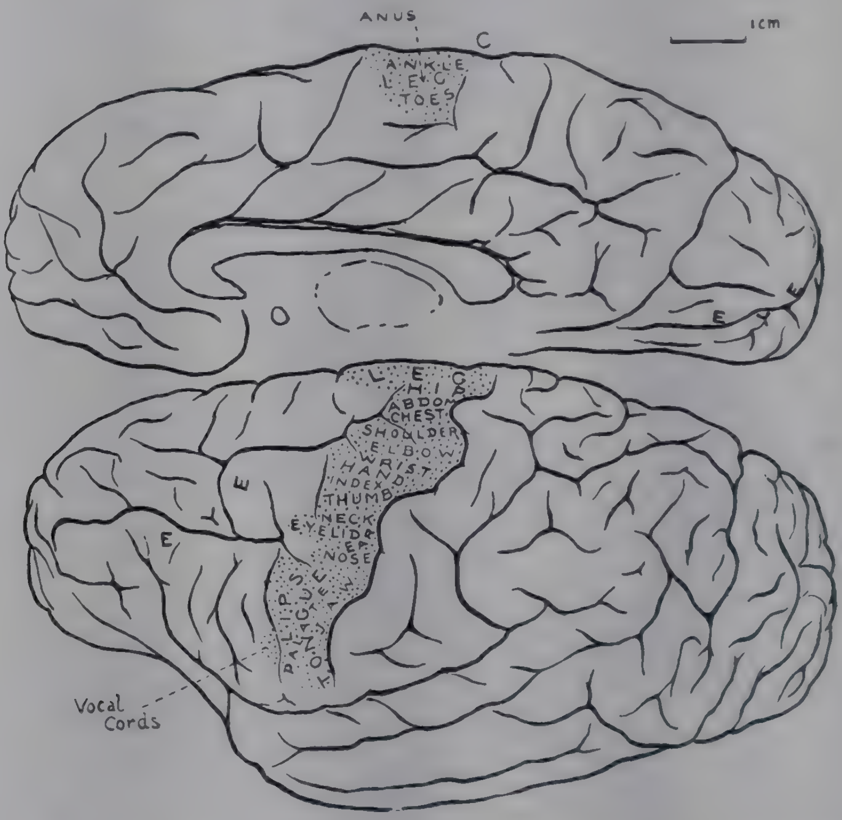


FIG. 143.—The motor area of the cortex of a gorilla as determined by motor responses to electrical stimulation. The responses are indicated on the diagram. C, opposite end of sulcus centralis. (From Leyton and Sherrington. *Quarterly Journal of Experimental Physiology,* **1917, 11**.)

Stimulation experiments show that, broadly speaking, the main parts of the body musculature are represented in certain parts of the motor area, and that the representation follows a definite pattern. However, the minuter localization in the motor area, as determined in primates, is subject to a marked temporal instability in the individual and apparently to anatomical variations in the species. The temporal instability may be related to variations in the resting electrical activity that the cortex shows.

Because of the direct connection between the motor area and the final common paths, the former must be concerned in the functional control of the skeletal muscles. However, there is evidence that the motor area is of limited importance in some animals, for example, the Ungulata. In these animals the area is small and its destruction (sheep) is without evident effect on locomotion, even immediately after the operation. In Carnivora the motor area is of somewhat greater importance in the control of skeletal muscles, but even in these animals its destruction is attended by only temporary motor disturbance. In fact, complete locomotor function may be regained after bilateral decortication. In anthropoids the motor area is still larger and more important, but the paralysis that follows its destruction usually disappears; indeed, recovery may follow destruction of both areas. In man

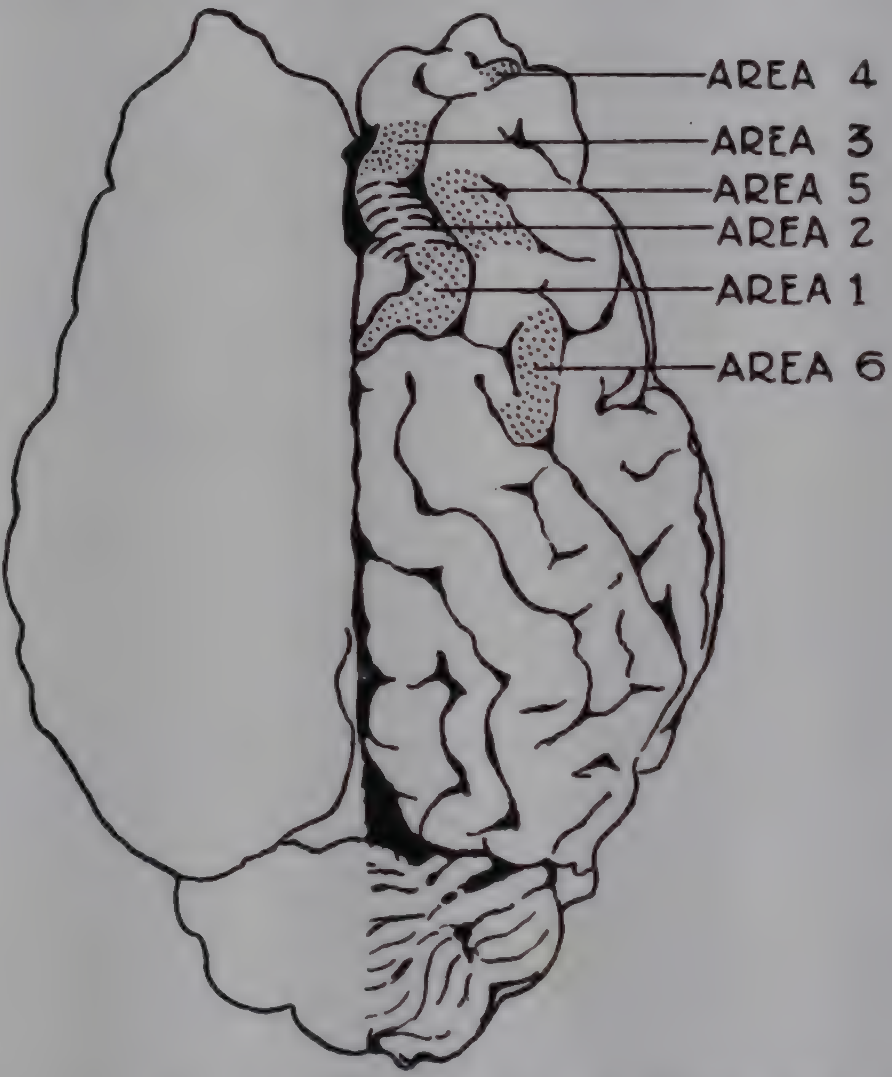


FIG. 144.—Dorsal surface of sheep's brain to show the location of the motor areas. Areas 1 and 2, for movements of the extremities; Areas 3, for movements of the head and eyes to the opposite side; Area 4, for movements of the face muscles of the opposite side (the full extent of this area could not be shown in this illustration); Area 5, for movements of the face muscles of the same side; Area 6, histologically of the motor type of cortex, but nonresponsive on stimulation. (Sketched from a half-tone illustration in *Archives of Neurology and Psychiatry*, 1922, 7.)

destruction of the motor area or of the pyramidal tract results in severe motor paralysis from which full recovery practically never occurs. However, it is to be noted that even in man partial recovery often follows.

Extrapyramidal Cortical Projections. Various lines of evidence indicate quite clearly that in mammals including primates a considerable cortical control of the skeletal muscles must take place through paths other than the corticospinal system. There are a number of motor projections from the cortex which make up an *extrapyramidal system.* These have levels of integration both in the cerebral cortex and in the upper part of the brain-stem. The impulses which they transmit reach the motoneurons via the rubrospinal and the reticulospinal tracts. They are concerned in postural adjustments, and in the case of one component of the reticulospinal tract (p. 598) with autonomic activity. The extrapyramidal system involves, in part, pathways that pass through the cerebellum (Fig. 141). It is the extrapyramidal system, and not the pyramidal, whose interruption by experimental lesions or pathological processes leads to rigidity and other hypertonias. The normal suprabulbar inhibitory influence which is cut off in decerebrate rigidity is extrapyramidal in origin. Four extrapyramidal motor projections from the cerebral cortex are shown in Fig. 141.

Sensory Areas. The cerebral cortex contains bilaterally situated sensory areas or centers into which the sensory projection fibers discharge (Fig. 142). The following sensory areas are distinguished: (1) the somesthetic, or body sense, area; (2) the visual area; (3) the auditory area; and (4) the olfactory area. The first three areas are found in the neopallium; the olfactory area is situated in the archipallium.

Besides receiving fibers that discharge sensory impulses into them, the sensory areas send out association fibers, short and long, to near and remote parts of the cortex, which parts are themselves interconnected by numerous complexly arranged fibers. By means of these various fibers each part of the cortex is in potential physiological connection with every other part, including the motor areas. Furthermore, the sensory areas that receive radiations from the thalamus—somesthetic, visual, auditory—also send fibers to the thalamus. As previously noted, these fibers probably enable the cortex to exert a restraining influence over thalamic centers.

Somesthetic Area. This area receives impulses from the skin concerned with touch, warmth, cold, and the localization of pain; impulses concerned with taste; and impulses from muscles, tendons, and joints concerned with proprioceptive sensibility ("muscle sense"). Pain probably makes a primitive appeal to centers in the thalamus, but determining the location of pain and its intensity is a function of the cerebral cortex.

The principal experimental methods of studying the location of this area are (1) electrical stimulation of the cortex exposed under local anesthesia in conscious human patients; (2) the local application of strychnine to various regions of the exposed cortex, following which the animal bites, scratches, or otherwise signals the skin area to which the sensations aroused in the cortex are projected; and (3) the finding, by the detection of electrical changes, of the cortical area which receives afferent impulses from touch or pressure receptors in the skin. The area as delimited by the last method is probably smaller than that in which electrical stimulation will cause sensations and is certainly smaller than that defined by the method of strychninization.

In primates the body sense area is located in the posterior central (postcentral) gyrus, but it extends into the motor area as well. Stimulation of the somesthetic area in man usually gives projected sensations of numbness, tingling, touch, and movement without actual motor response. Sensations of pain, warmth, and cold are unusual.

Studies of the electrical changes occurring in the cerebral cortex as a result of cutaneous tactile, pressure, visual, and auditory stimuli have been made (Marshall, Woolsey, and Bard; Adrian, 1941, 1943). The electrical changes are amplified and led to a loudspeaker or to an oscillograph for visual examination and recording. The tactile or pressure receptors are stimulated manually, for example by a camel-hair brush or feather to move individual hairs or by a glass rod for pressure. The visual and auditory receptors are stimulated by flashes of light and sound. By such methods Adrian studied the afferent areas in the cerebral cortex of many species including the common ungulates.

The somesthetic area, or, as Adrian preferred to designate it, the somatic receiving area, for the rabbit, cat, dog, and monkey is shown in Fig. 145. In the diagram of the cat's brain the auditory and visual areas are also shown. The somatic, as well as the auditory and visual, receiving areas for the goat and pig are shown in Fig. 146. Cortical responses to thermal and pain stimuli were not detected. The representation of the different parts of the body in the cortex showed great stability. In general, it was evident that the somatic receiving area of the cortex is concerned with those parts of the body surface that are in closest contact with the outside world, such as the feet, face, lower lip (sheep), snout, nostril, and the exposed surfaces of the head, trunk, and limbs (carnivores). In ungulates the limbs and trunk were in general poorly represented in the cortex.

Visual Area. The fibers of the optic radiations arise in the lateral geniculate body of the thalamus and pass to the occipital part of the cortex, in which the visual area is located (Figs. 142, 145, 146). Into this area these fibers pour impulses that call forth visual sensations.

The fibers of the optic nerve originate from the ganglion cells of the retina. Most of them end in the lateral geniculate body, from which the visual path is continued to the visual area of the cerebral cortex. Some of the optic nerve fibers terminate in the anterior colliculus, which contains reflex centers for movements of the eye and the movements of accommodation. In animals with overlapping visual fields the fibers from the nasal portion of the retina decussate in the optic chiasma; those from the temporal portion do not cross.

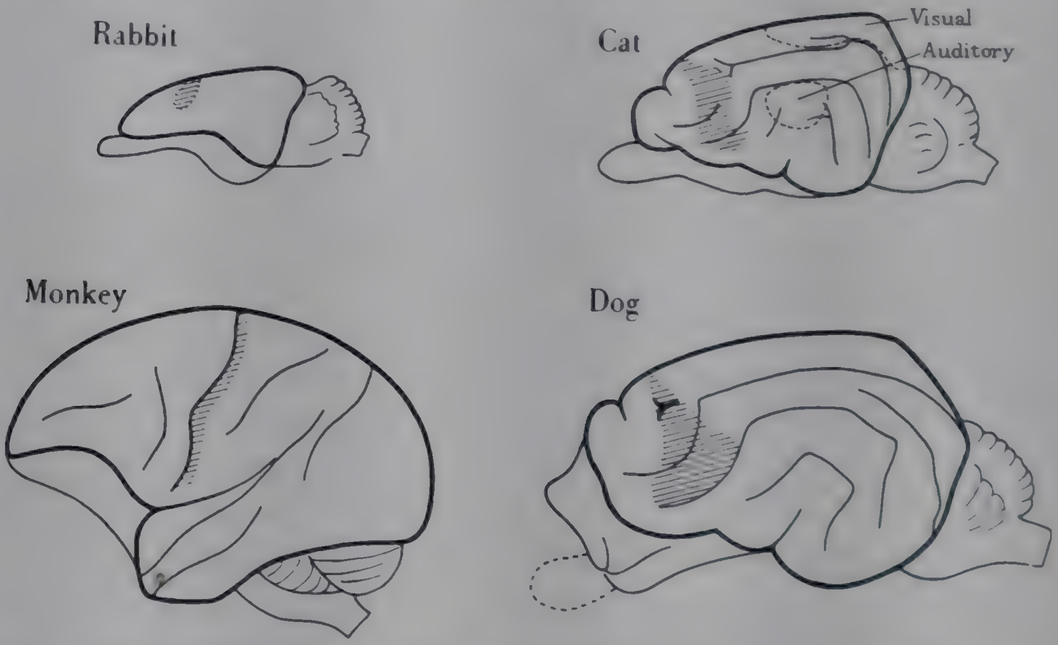


Fig. 145.—Location and relative size of the somatic receiving area (somesthetic area) in the cerebral cortex of the rabbit, cat, dog, and monkey. The auditory and visual areas are also indicated for the brain of the cat. (From Adrian, *Journal of Physiology*, 1941, **100**.)

Auditory Area. This area, located in the temporal lobe, receives the fibers of the auditory radiations from the medial geniculate body of the thalamus. Nerve impulses giving rise to auditory sensations are received in this area (Figs. 142, 145, 146).

The fibers of the cochlear nerve, the nerve of hearing, originate in the spiral ganglion of the organ of Corti and end in the cochlear nuclei of the pons. From these nuclei, fibers pass to the medial geniculate body of the thalamus. In addition, important auditory reflex connections exist in the posterior colliculus.

Olfactory Area. As previously stated, the cerebral cortex consists of an ancient part, the archipallium, and a more recently acquired part, the neopallium. The archipallium is relatively poorly developed in primates. It attains its greatest developments in the lowest mammals, especially the marsupials. The archipallium is dominated by the olfactory apparatus and comprises the hippocampus and hippocampal gyrus. In the region of the hippocampus the olfactory area is located. It receives projection fibers from the secondary olfactory center at the base of the olfactory bulb.

The fibers of the olfactory nerve originate from nerve cells located in the olfactory mucous membrane and terminate in the primary olfactory center, which is situated in the olfactory bulb. This primary center is in connection with the secondary olfactory center referred to above. In addition to sending projection fibers to the olfactory area in the cerebral cortex, the secondary olfactory center is concerned in olfactory reflexes.

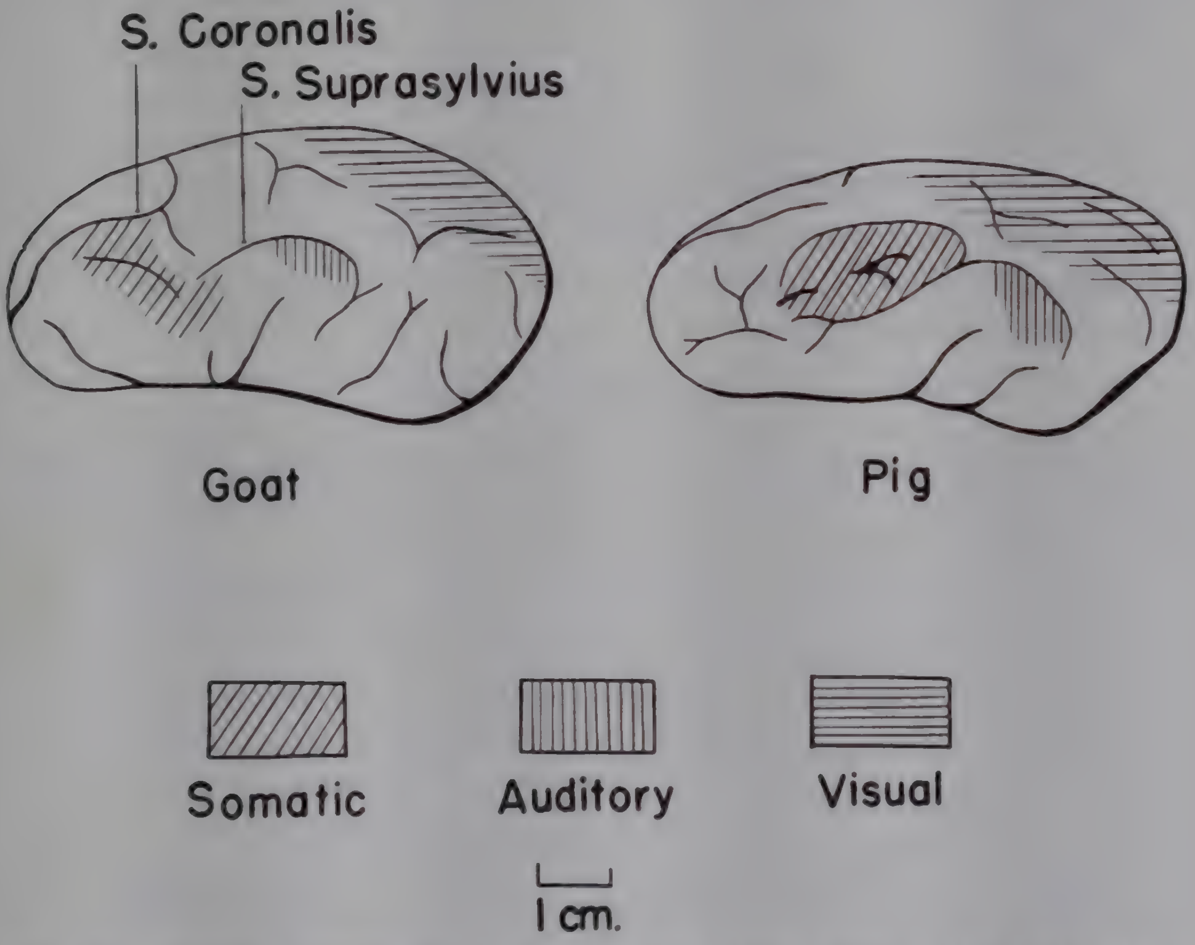


Fig. 146.—Somatic (somesthetic), auditory, and visual areas in the brain of the goat and pig. In the goat most of the somatic receiving area is supplied by receptors of the lips and snout. The connections are largely homolateral. The forefoot is usually represented and the hindfoot may be represented, in each case contralaterally. In the pig the whole somatic receiving area is supplied by receptors of the contralateral half of the snout. The margins of the visual area were not precisely determined. (Redrawn and slightly modified from Adrian, *Brain,* 1943, 66.)

Prefrontal Area. When the electrically excitable parts of the frontal lobe are deducted, what is left is the prefrontal area, also known as the frontal association area. It is the nonmotor, silent, or inexcitable part of the frontal lobe. The most remarkable thing about the brain of man is the enormous size of the prefrontal area. In all other mammals, including the anthropoids, it is much smaller. The prefrontal area is in connection with the brain-stem by ascending and descending fibers. The great prominence of the prefrontal cortex in man is doubtless correlated with his superior mental development, but in what way is not known. At one time this part of the brain was considered by many to be the seat of intelligence, but such a view is not held at the present time. The higher psychic functions are not localized exclusively in one part of the cerebral cortex. Clinical studies in man and experimental studies in monkeys indicate that deficits of the prefrontal area are manifested by restlessness, increased motor activity, changes of behavior, failure of memory for recent events, and other aberrations.

CONDITIONED REFLEXES

Reflexes may be divided into two groups. All spinal and brain-stem reflexes belong to the group of inborn, stereotyped, invariable reflexes that are peculiar to the species. The number of these is very great. The cardiovascular reflexes, the reflexes of respiration and digestion, the reflexes of metabolism and elimination, the postural and locomotor reflexes, and even that body of more complex reactions sometimes referred to as instincts, all belong to this group, many of which have been studied in previous chapters of this book. Reflexes of this kind were designated as unconditioned reflexes by Pavlov.

The other group includes all those reflexes that are gained by the individual in the course of its existence. These are the conditioned reflexes (Pavlov), so called because they depend on many conditions for their formation and maintenance. They are also known as individual or acquired reflexes and are—in many instances, at least—the same as those nervous reactions long known as associations. Briefly stated, a conditioned reflex is a habit. Because there is objection to the use of the term reflex to designate this type of nervous reaction, the term response may be substituted. Conditioned reflexes may be acquired either naturally or artificially, that is, experimentally. Following are examples of "natural" and "artificial" conditioned reflexes. When food is placed in the mouth of a dog, saliva is secreted. This is an inborn or unconditioned reflex. But as a dog develops he acquires a reflex that causes him to secrete saliva, if he is hungry, when he sees food with which he is familiar or smells food. This is a natural conditioned reflex.[1] If, when a dog is fed, a certain sound is made, for example, a whistle is blown, and this association of sound and food is frequently repeated, there comes a time when the sound alone is sufficient to cause the secretion of saliva. This is an artificial conditioned reflex. There is no fundamental difference between these two kinds of conditioned reflexes.

Conditioned reflexes develop in relation to an already present reflex, which may be either an inborn reflex or another conditioned reflex. The efferent side of the arc of the conditioned reflex is the same as that of the inborn reflex on which it is built. The afferent sides of the two arcs are not the same. The afferent side of the conditioned-reflex arc becomes attached to an already functional efferent side, which belongs to some inborn reflex. Since reflexes of the latter kind call forth either motion or secretion, it is evident that conditioned reflexes, utilizing as they do the efferent machinery of these inborn reflexes, can do no more than this. The number of unconditioned reflexes upon which conditioned reflexes may be superimposed is theoretically as great as the number of unconditioned reflexes in the body. Actually, conditioned reflexes have been developed in relation to cardiovascular reflexes; alimentary reflexes, motor and secretory; pupillary reflexes; reflexes of the skeletal motor system; and others. Pavlov and his co-workers usually used the salivary secretory reflex, which is a relatively simple part of a much more complicated and fundamental alimentary reflex. The unconditioned stimulus was food. The experimental animal was the dog. Liddell and co-workers have made extensive studies on the conditioned motor reflex of the forelimb—a defensive reflex. The animal that has been studied most thoroughly is the sheep, but studies have been made also on the goat, pig, dog, and rabbit. The unconditioned stimulus used in these experiments is an induction shock of moderate strength.

The stimuli in consequence of which conditioned reflexes may be developed, that is, the effective conditioned stimuli, are numerous. Thus visual, olfactory, auditory, gustatory, tactual, proprioceptive, and other stimuli have been used.

According to Pavlov, the formation and maintenance of conditioned reflexes are dependent upon the cerebral cortex, whose complete removal not only abolishes all such reflexes but makes the acquisition of additional ones impossible. The removal of localized areas causes less severe effects; after a period of disturbance of existing conditioned reflexes, they return. More recent work has shown that the mediation of learned activity is not an exclusive function of the cerebral cortex but is to a small extent a function of subcortical centers.

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[1] Herbivores fail to develop the conditioned salivary reflex.

Much of the work on conditioned reflexes has been done in the laboratories of Pavlov. The results of this work have been made readily available to readers of English in two books translated from Pavlov's Russian writings. In this country Liddell and co-workers have made important studies in which several species of farm animals have been utilized.

Circumstances Underlying the Formation of Conditioned Reflexes. In order that a conditioned reflex may be established, it is necessary that certain fundamental requirements be met. Some of these are as follows:

1. There must be substantial temporal coincidence between the hitherto neutral stimulus that is to be developed into a conditioned stimulus, or signal, and the unconditioned stimulus. When the temporal relations of the two stimuli—for example, the blast of a whistle and food—are exactly the same, the reflex that develops, after a number of trials, is designated as a simultaneous conditioned reflex. But the previously neutral stimulus may precede the application of the unconditioned stimulus (food), and yet a conditioned reflex will be developed in due time if the former stimulus is continued up to the time of application of the latter. Such a reaction is known as a delayed conditioned reflex. It has a latent period equal to the interval between the beginning of the neutral stimulus and the beginning of the unconditioned stimulus. Furthermore, it is possible to develop a conditioned reflex even though an interval is allowed to elapse between the cessation of the neutral stimulus and the application of the unconditioned stimulus. The "trace" of the neutral stimulus in the nervous system becomes, after frequent repetition, sufficiently strong to call forth the conditioned reflex. On the contrary, if the unconditioned stimulus is applied first and the neutral stimulus afterward, the conditioned reflex fails to develop.

2. The nervous system must be in a lively state. If the animal is drowsy the conditioned reflex develops very slowly or, occasionally, not at all. Furthermore, the animal must be reasonably well removed from the influence of stimuli other than the one that is being developed into a conditioned stimulus. Thus the state of alert quiet of the animal is not unknowingly disturbed. Isolation of the animal from its environment is accomplished by placing it in an insulated room (Fig. 147). The experiment is carried on by an operator in an adjoining room, who observes the animal through a periscope or a window and manipulates a system of controls by which the stimuli are applied. The responses of the animal are observed or recorded graphically.

3. The animal must be in good health and thus free from the disturbing influence of pathological stimuli.

4. The stimulus that is to be developed into a conditioned stimulus should, for best results, be neutral, or as nearly so as possible, at the outset. Strong or unusual stimuli become effective with difficulty because they themselves evoke unconditioned responses. The stimulus for an unconditioned reflex cannot be changed into the stimulus for a conditioned reflex unless the former reflex is physiologically weaker and less important than the latter. Because the alimentary reflex is biologically so strong it is possible to transform even nocuous stimuli into conditioned stimuli for this reflex. Ordinarily, however, quite innocuous and previously inert stimuli are employed.

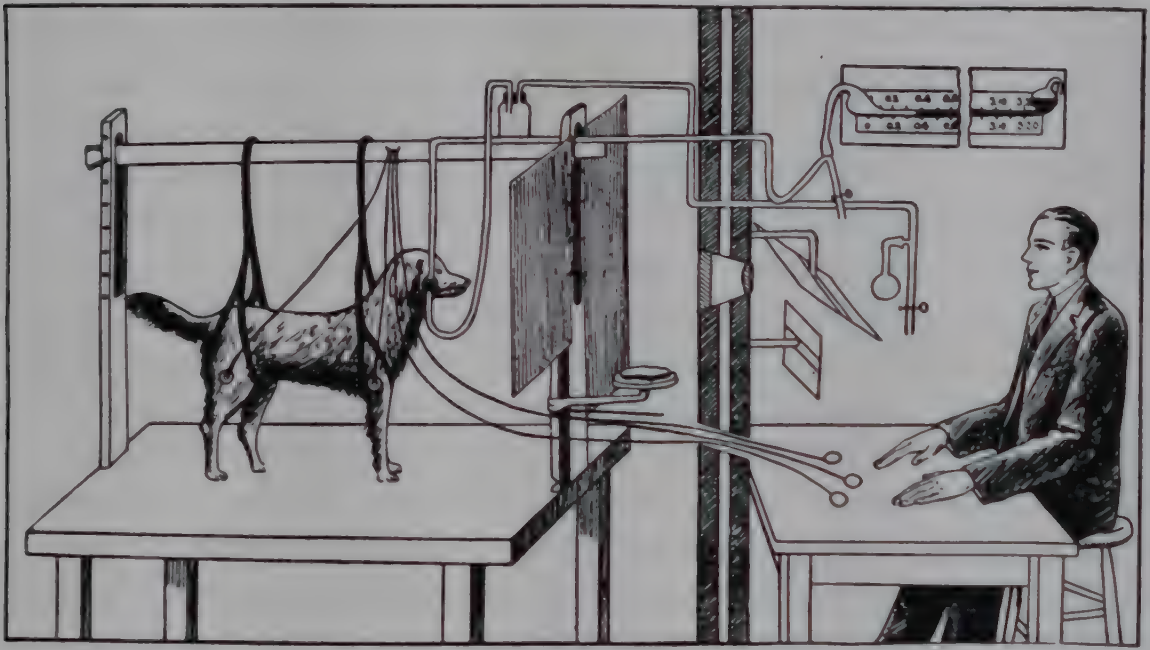

Fig. 147.—Diagram of arrangements for studying conditioned reflexes in the dog. A soundproof, opaque partition separates the dog from the observer. The devices for observing and stimulating the animal and determining the salivary response are shown. (From Pavlov, *Lectures on Conditioned Reflexes*, International Publishers Company.)

Properties of Conditioned Reflexes. Conditioned reflexes present many features, some of which are similar to those of inborn reflexes and some different. Following are several of the properties of conditioned reflexes:

1. It is possible to develop a conditioned reflex as the result of the application of one stimulus, for example, sound, and a conditioned reflex as the result of the application of another stimulus, for example, a flash of light, and to utilize in both reflexes the same efferent machinery, for example, the salivary mechanism. When the two stimuli are

applied simultaneously, the response is greater than when they are applied independently. This property is spoken of as reinforcement and is similar to reinforcement of unconditioned reflexes.

2. If a conditioned reflex is to be kept at a constant strength, the conditioned and unconditioned stimuli must be regularly applied as during the formation of the reflex. Otherwise it gradually weakens and finally disappears.

3. If the conditioned stimulus is applied repeatedly and in rapid succession, but the unconditioned stimulus is withheld, the conditioned reflex is greatly weakened or, in extreme cases, extinguished. Experimentally extinguished conditioned reflexes usually regenerate spontaneously in several hours. If the reflex is repeatedly extinguished, it finally disappears completely. This is in contrast with unconditioned reflexes, which cannot be extinguished.

4. By the method of conditioned reflexes it is possible to test the ability of animals to differentiate between stimuli. The ability to differentiate between stimuli affecting different receptors, for example, the eye and the ear, is perfect, so that a conditioned reflex developed for light cannot be called forth by sound. But the ability of animals to differentiate between stimuli affecting the same receptor is not so perfect, and varies in different species. If a tone of 1000 vibrations per second is developed as a conditioned stimulus for the dog, it is found that tones of neighboring frequencies above or below 1000 also call forth the reflex. However, it is possible experimentally to extinguish these accessory reflexes and thus to make the original reflex more specific. In this way it can be shown that although a tone of 1000 vibrations will stimulate salivary secretion, a tone as near as 1012 vibrations will be ineffective. By the same general method it has apparently been shown that the dog is able to distinguish sounds up to 100,000 vibrations per second. The limit of man's ability is much lower than this. Similarly it has been shown that although degrees of luminosity are well differentiated by the dog, the ability to differentiate colors is poorly developed or, in most dogs, entirely absent. Color-blindness would therefore appear to be the prevailing condition in dogs. The discrimination of different degrees of cutaneous thermal stimuli and of different tactile stimuli is readily made by the dog.

SLEEP

Ordinary sleep is a condition characterized by (1) loss of ability critically to analyze changes in the environment; (2) increased threshold to sensory stimulation; and (3) ability to awaken. All animals have periods of rest following periods of activity. Sleep is usually an accompaniment of the rest period. Although sleep is characterized by muscular inactivity, the latter is only relative, as is shown by graphic records and motion pictures of sleeping individuals.

As regards the relation of the periods of rest to the periods of activity, animals are of three types: monophasic, polyphasic, and intermediate. Monophasic animals typically have a long period of rest at night following the activities of the day. Man is by nature monophasic. The same is true of most birds. Polyphasic animals show several alternating periods of rest and activity in the 24 hours. Many of the wild mammals are of this kind. Animals of intermediate type show alternating periods of rest and activity during the day but one long period of relative rest at night. Most of the domestic animals belong to this class. Animals that depend largely on optical stimuli for information about their environment tend to be inactive at night, whereas those that depend largely on olfactory and tactile stimuli are apt to show considerable activity in the dark.

Physiological Changes in Sleep. In addition to the accompaniments of sleep mentioned above, a number of others may be listed, knowledge of which has been gained, in the main, from studies on human beings. The heart rate decreases, and the blood pressure usually falls. It had long been believed that anemia of the brain is present, but careful records of changes in brain volume have not supported this view. The breathing movements are regular in rate and amplitude. The partial pressure of carbon dioxide in the alveolar air is increased. The alkali reserve of the blood is little affected, but the *p*H of the blood is slightly reduced. The amount of urine secreted is usually smaller, and the metabolic rate is decreased. The threshold of sensory stimulation is increased; in fact, some reflexes, including the knee-jerk and the righting reflexes, disappear.

Theories of Sleep. A number of theories have been proposed to explain sleep, but, as is evident from Kleitman's review of the literature, a fully acceptable one it lacking. On the basis of his work, Kleitman has proposed a theory whose salient features may be summarized as follows: The neuromuscular mechanism of postural tonus becomes fatigued, which results in a marked decrease in the number of proprioceptive impulses. The highest cerebral centers, thus partly isolated from afferent stimulation, fall into a condition of readily reversible inactivity known as sleep. Sleep is favored by any condition that results in muscular relaxation. Thus while fatigue of the tonus mechanism is the usual cause of such relaxation, it is not the necessary cause. Sleep and wakefulness in their diurnal manifestations are largely conditioned responses.

There are several chemical theories of sleep. The *hypnotoxin* theory of Piéron has been reinvestigated by Schnedorf and Ivy. Cerebrospinal fluid from dogs kept awake for days will induce profound sleep when injected intracisternally into normal dogs. Further evidence is required, however, before it can be said that the sleep so induced is caused by a specific sleep-producing substance in the fluid from the fatigued dogs.

Chapter XXXV

THE AUTONOMIC NERVOUS SYSTEM

THE autonomic nervous system is that division of the nervous system which supplies efferent fibers to the glands and the visceral musculature of the body. This is in contrast with the somatic division, which supplies the striated musculature. The nomenclature of the system of nerves under consideration is not fully settled. The terminology used here is in part that of Langley. The autonomic nervous system is made up of two major divisions: the sympathetic or thoracolumbar and the parasympathetic or craniosacral. The parasympathetic division comprises the following outflows from the central nervous system: hypothalamic, tectal, bulbar, and sacral. The first three together are sometimes referred to as the cranial portion of the parasympathetic. The various divisions of the autonomic nervous system are shown in the accompanying schema.

- **Autonomic Nervous System**
  - **Sympathetic (Thoracolumbar)**
  - **Parasympathetic (Craniosacral)**
    - **Cranial**
      - **Hypothalamic**
      - **Tectal**
      - **Bulbar**
    - **Sacral**

In Langley's terminology the autonomic nervous system is entirely efferent and peripheral. It is now recognized, however, that this conception is inadequate and that the terminology must be enlarged to include the central origins and pathways, as well as the afferent channels, concerned in the working of the system. Some of the afferent channels are specificially related to the functioning of the autonomic system, for example, the sinus and aortic nerves; whereas others carry impulses that affect both the somatic and the autonomic divisions. A close functional relationship thus exists between the autonomic and somatic divisions of the nervous system.

The efferent part of the autonomic nervous system supplies the glands and visceral musculature of the body. Most of these structures have a double innervation, which comes in part from the parasympathetic and in part from the sympathetic. On a number of the organs the action of the two sets of nerves is antagonistic, but the older concept of a well-defined, balanced antagonism between the parasympathetic and sympathetic systems is being challenged (Hare, Ingram). Tonic action is a feature of a number of the autonomic efferent channels.

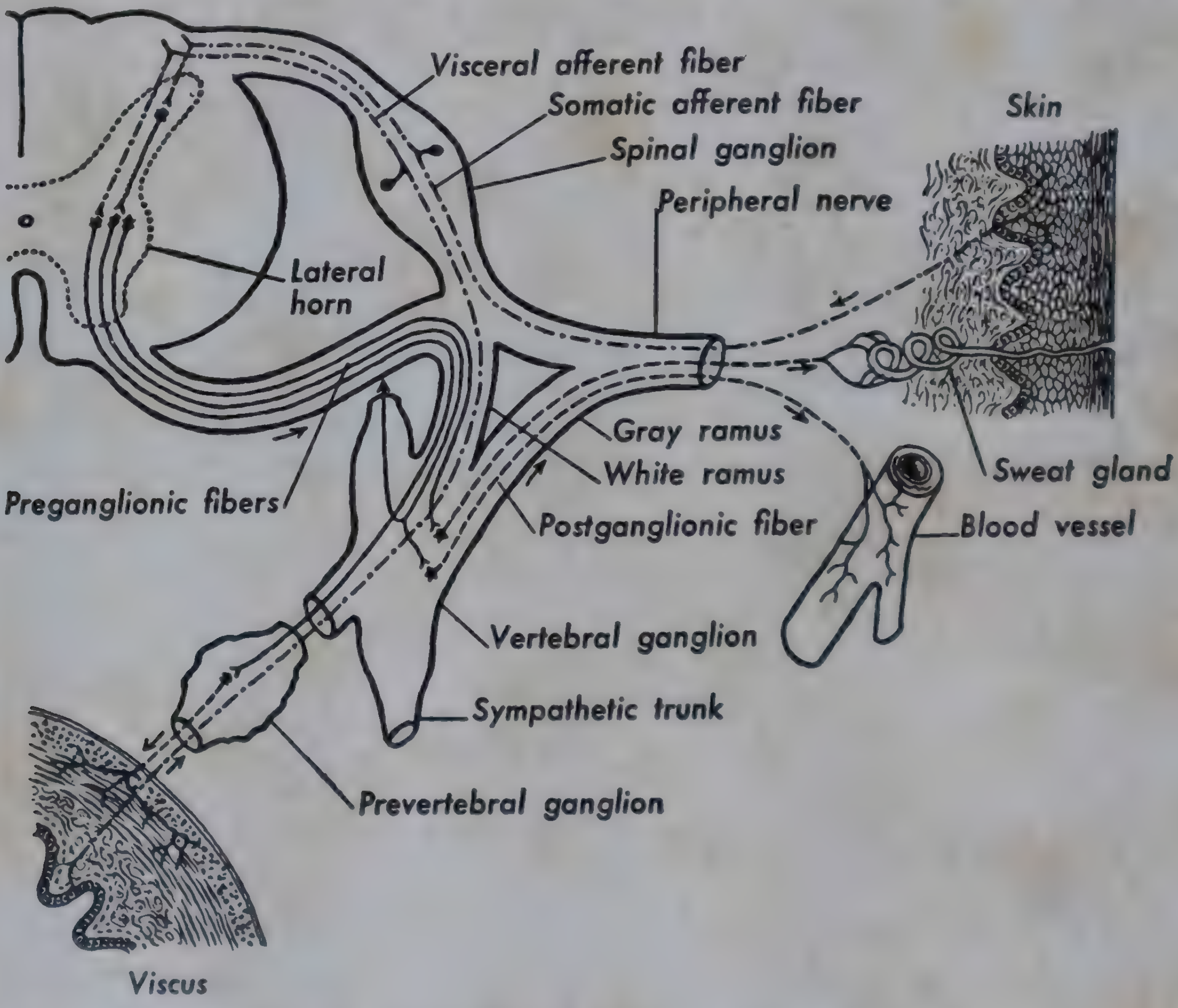
Visceral afferent fiber
Somatic afferent fiber
Skin
Spinal ganglion
Peripheral nerve
Lateral horn
Gray ramus
White ramus
Sweat gland
Preganglionic fibers
Postganglionic fiber
Blood vessel
Vertebral ganglion
Sympathetic trunk
Prevertebral ganglion
Viscus

FIG. 148.—Diagrammatic representation of the relation of sympathetic neurons to afferent fibers (somatic and visceral), spinal cord, sympathetic trunk, and effectors (sweat gland, blood vessel, viscus). Preganglionic fibers are shown in solid lines, postganglionic fibers in broken lines, afferent fibers in dot-and-dash lines. Arrows indicate the direction of conduction. (From Bailey's *Text-Book of Histology*, The Williams and Wilkins Company.)

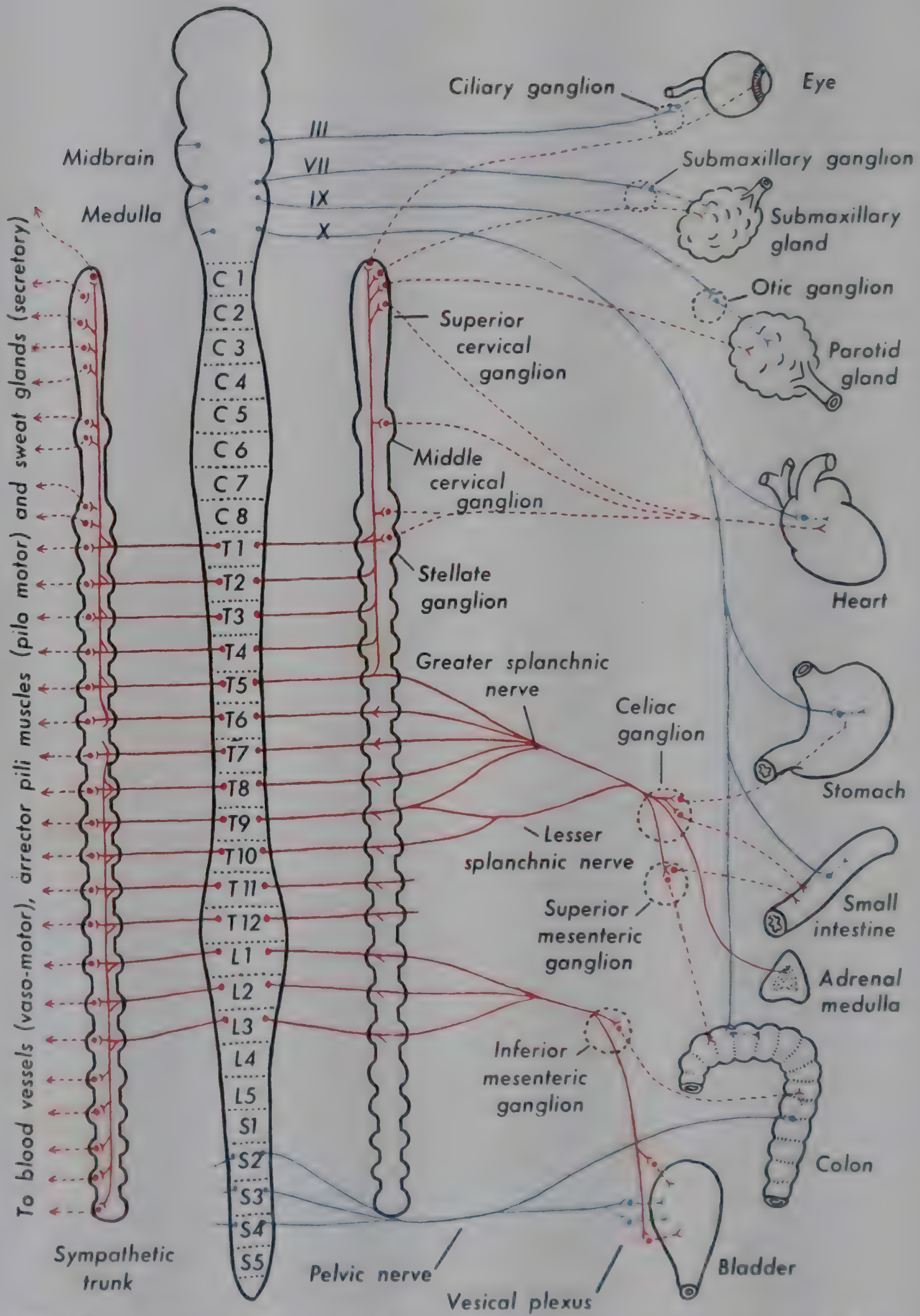
Ciliary ganglion
Eye
III
VII
IX
X
Midbrain
Medulla
Submaxillary ganglion
Submaxillary gland
Otic ganglion
Parotid gland
To blood vessels (vaso-motor), arrector pili muscles (pilo motor) and sweat glands (secretory)
C1
C2
C3
C4
C5
C6
C7
C8
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
L1
L2
L3
L4
L5
S1
S2
S3
S4
S5
Superior cervical ganglion
Middle cervical ganglion
Stellate ganglion
Heart
Greater splanchnic nerve
Celiac ganglion
Stomach
Lesser splanchnic nerve
Superior mesenteric ganglion
Small intestine
Adrenal medulla
Inferior mesenteric ganglion
Colon
Bladder
Sympathetic trunk
Pelvic nerve
Vesical plexus

FIG. 149.—Diagrammatic representation of the autonomic nervous system (efferent pathways). Nerves to blood vessels, arrector pili muscles, and sweat glands are shown only on the left side of the figure. Nerves to other structures appear only on the right side of the figure. The sympathetic division is shown in red, the parasympathetic in blue. Preganglionic fibers are shown by solid lines; postganglionic fibers by broken lines. (From Bailey's *Text-Book of Histology*. The Williams and Wilkins Company.)

After leaving the central nervous system, the nervous pathways to skeletal muscle run an unbroken course to their destination. This is not true of the nervous pathways to glands and visceral muscle. All the fibers of these latter pathways, the efferent fibers of the autonomic nervous system, are interrupted somewhere in their peripheral course by making synaptic junctions with nerve cells in autonomic ganglia, from which new axons arise to run to their destination. Those autonomic nerve fibers that run from the central nervous system to the autonomic ganglia are designated as preganglionic fibers; those that run from the autonomic ganglia to the place of termination of the pathway are known as postganglionic fibers (Fig. 148). Preganglionic fibers are myelinated; postganglionic fibers are generally nonmyelinated.

The relationship of sympathetic neurons to afferent channels, spinal cord, sympathetic trunk, and effectors is shown in Fig. 148.

The further discussions of the autonomic nervous system will be given according to its major divisions. For more detailed information regarding the autonomic nerve supply of the different organs, the parts of this book devoted to discussions of these organs should be consulted. Many facts regarding the efferent components of the autonomic nervous system are shown diagrammatically in Fig. 149.

THORACOLUMBAR DIVISION OR SYMPATHETIC SYSTEM

The sympathetic system is that part of the autonomic nervous system whose preganglionic fibers issue from the spinal cord in the ventral roots of the spinal nerves from the first thoracic to the fourth lumbar (dog, cat). The ganglia of the sympathetic system are divisible into two classes, vertebral or lateral and prevertebral or collateral. The vertebral ganglia occur in a double chain, the sympathetic trunks, which extend along the ventral surface of the vertebral column from the base of the skull to the tail. They are segmentally arranged except in the cervical region, where the number is reduced to two or three. The prevertebral ganglia are scattered among the viscera and comprise chiefly the celiac or semilunar, the anterior mesenteric, and the posterior mesenteric ganglia.

Connecting the sympathetic chain with the spinal nerves from the first thoracic to the fourth lumbar are the *white rami*, which consist of preganglionic fibers, whose place of origin is the intermediolateral cell column of the spinal cord. Entering the sympathetic chain, these fibers run up or down the chain and make synaptic junction with nerve cells in several vertebral ganglia, or leave the chain and pass, in the splanchnic nerves, to the prevertebral ganglia, where they terminate in synaptic relation to nerve cells. Thus some preganglionic fibers of the sympathetic system terminate in the vertebral ganglia, whereas others terminate in the prevertebral ganglia. From the nerve cells in the sympathetic ganglia, postganglionic fibers arise and run to their destination.

The Course of the Postganglionic Fibers. Most of the postganglionic fibers originating in the *vertebral ganglia* pass to the spinal nerves of the corresponding segments and are distributed to the skin as vasoconstrictor fibers, secretory fibers to the sweat glands, and motor fibers to the smooth muscle of the skin (pilomotor fibers). These postganglionic fibers on their way to the spinal nerves are grouped into strands known as *gray rami,* there being a gray ramus for each spinal nerve. However, all postganglionic fibers originating in the vertebral ganglia do not return to spinal nerves; many of them in the cervical region run in plexuses to structures in the head and chest, some of which are as follows: (1) the pupil, whose radial muscle fibers receive motor innervation; (2) the salivary glands, which receive secretory fibers; (3) certain blood vessels of the head, which receive constrictor fibers; (4) the heart, which receives accelerator and vasomotor fibers; and (5) the bronchi, which receive dilator fibers.

The postganglionic fibers originating in the *prevertebral ganglia* have a very extensive distribution to the abdominal and pelvic organs Among the structures supplied are: the gastric glands, pancreas, liver, and probably the intestinal glands; and the smooth muscle in the walls of the esophagus, stomach, intestine, spleen, biliary system, ureter, urinary bladder, reproductive organs, and splanchnic blood vessels. For the action of these nerve fibers, the discussions on the physiology of the individual organs should be consulted.

Functions of the Sympathetic Ganglia. From the foregoing it is evident that the sympathetic ganglia represent points of synaptic junction in the paths of the thoracolumbar autonomic outflow. The cells of origin of the preganglionic fibers are situated in the lateral gray columns of the spinal cord. The cells of origin of the postganglionic fibers are located in the vertebral and prevertebral ganglia. Those preganglionic fibers that make synaptic junction in the prevertebral ganglia pass unbroken through the main sympathetic chain. Thus here as elsewhere in the autonomic system the efferent nervous paths always consist of two neurons.

The number of postganglionic fibers is much greater than the number of preganglionic fibers (Kuntz). This is explained by the finding that each preganglionic fiber enters into synaptic relation with many (about 15 in the anterior cervical ganglion of the cat) ganglionic nerve cells, from which postganglionic fibers originate. This fact indicates what is probably the main function of the sympathetic ganglia: they bring single neurons into physiological connection with many neurons and thus permit diffusion or divergence of nerve impulses to many effector organs. In this light the preganglionic neurons appear as interneurons, different from ordinary interneurons mainly in that their fibers leave the central nervous system to end around nerve cells that have wandered toward the periphery—that is, the nerve cells in the sympathetic ganglia.

Another possible function of sympathetic ganglia is to alter the frequency of the nerve impulses reaching them from the central nervous system to meet the needs of the structures innervated (Cannon). According to this theory, nerve impulses reach the ganglia at varying frequencies but leave the ganglia at a relatively fixed frequency, which is optimal for the tissue innervated.

Still another possible function of the sympathetic ganglia may be mentioned. The old view that the ganglia can serve as centers of reflex action finds support in modern work (Schwartz). It was found in experiments on cats that the stellate ganglion could mediate reflexes when completely separated from the central nervous system. That the observations could not be explained in terms of the axon reflex was indicated by the fact that the reflexes were abolished by the injection of nicotine. Hence a synapse was indicated by the evidence, for nicotine paralyzes synapses in the autonomic system.

Chemical Transmission. Recent work shows that stimulation of preganglionic sympathetic fibers results in the liberation of acetylcholine in sympathetic ganglia. The place of its formation appears to be the synapse. It has been postulated that acetylcholine acts as a chemical transmitter of nerve effects from the terminations of the preganglionic fibers to the ganglionic nerve cells. But the evidence for chemical transmission in sympathetic ganglia is not conclusive (Eccles, Fulton). Acetylcholine may serve other functions in the ganglia.

Significance of the Sympathetic System. In spite of the wide distribution and numerous functions of nerve fibers belonging to the sympathetic division of the autonomic nervous system, this division can be dispensed with entirely and the animal still live in a state of health, at least in a protected environment. This was shown in cats by Cannon and co-workers, who accomplished bilateral removal of the sympathetic chains, thus breaking all sympathetic pathways. Cats so treated lived, in a state of health, for many months in the protected environment of the laboratory (Fig. 150). Reproduction took place but milk secretion was interfered with. Emotional excitement caused no erection of hairs and no consistent increase in blood sugar. The animals were sensitive to cold. Basal metabolism was slightly lowered. Further observations on reproductive functions in sympathectomized cats have been made by Simeone and Ross. Abortions and stillbirths were common. Completely sympathectomized cats are able to do much less muscular work (running in treadmill) without fatigue than before the operation. The cardiac acceleration accompanying exercise is less in sympathectomized cats (Hodes). Evidently cats lacking the sympathetic system are less able than normal cats to withstand unfavorable environmental conditions and other circumstances that put the physiological mechanisms under stress.

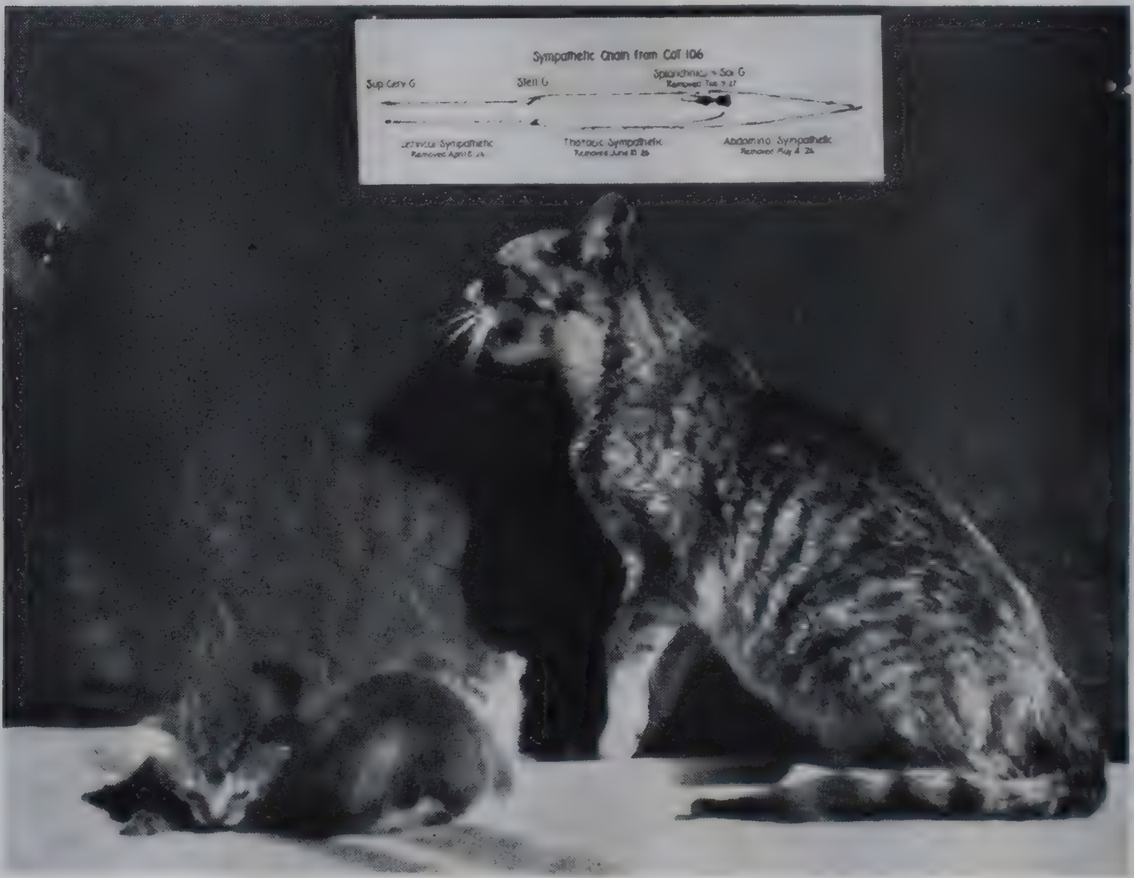

Fig. 150.—Photograph of a cat from which the sympathetic chains, including the semilunar ganglia, had been removed. The parts removed are mounted on the card above. Her kittens born after she was completely sympathectomized are also shown. Although a barking dog has aroused the cat to protect her young, there is no erection of hairs on the cat. (Courtesy of Dr. W. B. Cannon.)

Dogs show less effects of sympathectomy than do cats. The general behavior of sympathectomized dogs is normal. The capacity to stand intense exercise is not diminished (Brouha, Cannon, and Dill, 1936). Heat regulation is essentially normal. However, sympathectomized dogs are much more sensitive to injected insulin than normal control dogs (McDonough). This sensitivity results merely from adrenal denervation and therefore failure to secrete adrenaline, for dogs from which the adrenal medulla has been removed show the same sensitivity to insulin as dogs from which the sympathetic has been removed (Brouha, Cannon, and Dill, 1939).

Papez, Jensen, and Dukes have reported on two dogs, a male and a female, that had been submitted to complete bilateral sympathectomy. No changes in the behavior of the dogs were noted. About a year after the operation they were successfully bred to each other. As a result of this mating two normal pups were born, and were nursed in a normal manner. After two years the animals were autopsied to determine the nature and degree of nerve regeneration. Some pseudoregeneration of the sympathetic trunks and splanchnic nerves was found, but histological examination showed that the number of regenerated splanchnic and sympathetic nerve fibers was small—much smaller than gross examination of the false nerve trunks would suggest.

The foregoing considerations, especially as applied to cats, help to indicate the main function of the sympathetic nervous system. It is in the emergencies of life that it is most useful. In the struggle for existence the operation of the somatic mechanisms results inevitably in changes in the internal environment or fluid matrix of the body. These changes would be harmful if they were not promptly corrected. It is the function of the sympathetic system together with the adrenal medulla (sympathico-adrenal system) to bring the internal environment promptly back to its normal condition of stability and constancy; in short, to maintain *homeostasis*. In carrying out its function of preserving homeostasis, the sympathetic system acts as a whole, or diffusely. The sympathectomized animal lacks this emergency mechanism so important in the maintenance of homeostasis. The explanation of the fact that the dog is so little affected by removal of a large part of his homeostatic mechanism (sympathectomy) is probably seen in the other physiological mechanisms, not controlled by the sympathetic, that have been emphasized in the development of the dog as a running animal (McDonough). Some of these are large heart and lungs in relation to body size, large blood volume and high hemoglobin content, large vaporizing surface (mouth and tongue), and ease with which shivering occurs.

In addition to this emergency function, the sympathetic carries on other activities in the organism. These are for the most part tonic, and are concerned in the maintenance of heart rate, blood pressure, bronchial size, pupillary size, and other physiological states. Apparently in carrying on these functions in the quiet animal not all of the preganglionic fibers are conducting. The number in action can be increased or decreased reflexly. If an emergency arises many, probably all, go into action. Some of the sympathetic pathways are completely quiet at times. This is true of those to the sweat glands and smooth muscle in the skin.

PARASYMPATHETIC OR CRANIOSACRAL DIVISION

Hypothalamic Outflow. Preganglionic fibers arising from nerve cells in the supraoptic and other hypothalamic nuclei concerned with parasympathetic functions supply innervation to the posterior lobe of the pituitary body. Thus the secretion of the several hormones produced by the posterior lobe is brought under nervous control.

Tectal Outflow. The preganglionic fibers of this part of the autonomic nervous system arise in the visceral motor, or Edinger-Westphal, nucleus of the midbrain and run in the oculomotor nerve to the ciliary ganglion. Here they terminate in synaptic relation with nerve cells giving origin to postganglionic fibers, which supply motor innervation to the sphincter pupillae and the ciliary muscles of the eye.

Bulbar Outflow. Bulbar autonomic fibers are found in the following cranial nerves: facial, glossopharyngeal, vagus, and accessory.

Autonomic Fibers in the Facial Nerve. One group of preganglionic fibers, originating in a salivary secretory center in the medulla, runs in the chorda tympani to the submaxillary ganglion, from whose cells postganglionic fibers arise and pass to the submaxillary and sublingual glands. These fibers are secretory and probably vasodilator in function.

The other preganglionic fibers of the facial nerve reach the sphenopalatine ganglion via the greater superficial petrosal nerve, where they terminate. From nerve cells in this ganglion postganglionic fibers arise and supply secretory nerves to the lacrimal glands, and vasodilator and secretory nerves to the blood vessels and glands of the mucosa of the nasal and palatine regions.

Autonomic Fibers in the Glossopharyngeal Nerve. The preganglionic fibers of this nerve originate in a salivary secretory center in the medulla and pass, via the nervus tympanicus and the lesser superficial petrosal nerve, to the otic ganglion, where they end. From cells in this ganglion, nerve fibers arise and run in the auriculotemporal nerve to the parotid gland, to which they supply secretory and probably vasodilator innervation.

Autonomic Fibers in the Vagus and Accessory Nerves. The autonomic fibers of the *vagus* are numerous, have varied physiological functions, and are widely distributed. The preganglionic vagus fibers originate in the dorsal motor nucleus of the vagus, pass without interruption to the organs innervated, and there make synaptic junctions with ganglion cells. From these cells postganglionic fibers, usually short, arise and run to the terminations of the paths.

The musculature of the esophagus, stomach, small intestine, and upper part of the large intestine receives motor and, in some instances, inhibitory vagus innervation. The cells of origin of the postganglionic fibers are, according to current teaching, located in the intrinsic plexuses of these organs, especially the myenteric plexus. (For discussions and the literature, see Gaskell, Kuntz, Alvarez.)

The gastric glands, the pancreas, and possibly the duodenal glands receive secretory fibers from the vagus. The kidney also receives vagus innervation, but the significance of this is not clear.

The vagus supplies inhibitory and, to a less extent, parasympathetic accelerator fibers to the heart. The preganglionic fibers are long, whereas the postganglionic fibers are short, originating from nerve cells located in the heart itself. The trachea and bronchi receive constrictor fibers from the vagus.

The autonomic fibers of the *accessory nerve* are identical in origin and termination with the autonomic fibers of the vagus.

Sacral Outflow. The cells of origin of the sacral autonomic fibers are situated in the lateral part of the ventral gray column in the sacral region of the spinal cord. These fibers leave the spinal cord in the first three sacral nerves, from which they issue to form the pelvic nerve, or nervus erigens. Being preganglionic fibers, they make synaptic junctions with ganglion cells, which are scattered in proximity to the pelvic organs. From these cells postganglionic fibers arise and supply the arterioles of the rectum, anus, and external genital organs, and the musculature of the colon, rectum, anus, bladder, and external genital organs.

Significance of the Parasympathetic System. As previously noted, the sympathetic system is capable of acting as a unit. The four separate levels of parasympathetic outflow suggest that the different parts of the parasympathetic system are functionally unrelated to one another and would not show the unitary action of which the sympathetic is capable. These views are supported by various studies. Lack of unitary action may therefore be said to characterize parasympathetic responses. No useful purpose to the organism would be served by having such unrelated acts as salivary secretion, cardiac inhibition, gastrointestinal motor activity, and vascular engorgement of the genital organs occur simultaneously.

Isolated parasympathetic effects are further provided for by the relationship of the preganglionic fibers to the ganglia which give origin to the postganglionic fibers. These ganglia are situated within or close to the organs supplied, and the ratio of preganglionic fibers to ganglionic cells is only 1:2 (ciliary ganglion). When located within the organ (heart, intestine), the ganglia are widely distributed structures.

Broadly speaking, parasympathetic effects have to do with conservation and restoration of the resources and reserves of the organism.

CHEMICAL TRANSMISSION AT AUTONOMIC NERVE ENDINGS

It is now generally held on the basis of substantial evidence that the final transmission of nerve effects from autonomic nerve endings to the effector cells (muscle, gland) is by means of chemical substances released at the nerve endings when the nerves are conducting. Between the nerve ending and the effector a neurocellular junction—a sort of peripheral synapse—exists, and it is across this that chemical transmission occurs. The humoral transmitter of parasympathetic effects is acetylcholine; of sympathetic effects, usually an adrenalinelike substance, sympathin. However, some nerve fibers that are anatomically sympathetic yield acetylcholine upon stimulation (sweat secretory nerves of cat, sympathetic vasodilators). Nerve fibers liberating acetylcholine are designated as *cholinergic.* Those yielding the adrenalinelike substance are known as *adrenergic.* The methods used in studying these effects and the evidence derived from many experiments are summarized by Evans (1936). See also the book by Goodman and Gilman.

AFFERENT PATHS AND CENTRAL REPRESENTATION

In Langley's nomenclature the autonomic nervous system is entirely efferent. It is known, however, that afferent nerve fibers and nerve centers are functionally associated with this system, and they are now regarded as a part of it.

Afferent nerve fibers concerned in inaugurating autonomic responses are of two kinds: (1) somatic afferent components of the craniospinal nerves, and (2) visceral afferent components. The first group will receive no further consideration here. Fibers of the second group have their cells of origin in the craniospinal ganglia, contrary to a view sometimes held that the cells are located in autonomic ganglia. Therefore in regard to the location of their cell stations, these fibers do not differ from somatic afferent fibers. They pass through autonomic ganglia but without making functional connections therein. The impulses that they conduct do not ordinarily reach consciousness but excite reflex activity in the autonomic system. Examples of visceral afferent nerves are the sinus and aortic nerves and the numerous afferent fibers in the splanchnic nerves.

Many of the nerve centers concerned in the functioning of the autonomic system have been dealt with in appropriate places in this book. These centers are located particularly in the medulla oblongata. They are subject to reflex control and many of them are in tonic action.

In addition to the bulbar centers, there are hypothalamic centers for both sympathetic and parasympathetic functioning. The sympathetic center is located in the posterior part of the hypothalamus. It is the mechanism through which the emergency function of the sympathetic system is mediated (Bard, 1929). The parasympathetic centers are located in the middle and anterior portions of the hypothalamus.

Finally, there is cortical representation of the autonomic nervous system. This is believed to be the neurological basis of regional adjustments of autonomic activity to somatic functions.

VISCERAL PAIN

From observations made under local anesthesia it is known that the viscera can be handled, pinched, cut, or burned without the subject feeling any pain. Facts such as these gave rise to the idea that the viscera are insensitive. As a matter of fact, nerve impulses giving rise to pain can originate in the viscera if an *adequate stimulus* is present. The characteristics of the adequate stimuli for visceral pain are not well understood, but the following stimuli are effective: (1) distention, (2) strong contraction, especially if it is accompanied by ischemia, and (3) chemical substances.

Most impulses mediating visceral pain are conducted to the central nervous system via afferent fibers in the sympathetic nerves. The splanchnic nerve is very rich in afferent fibers. The cell bodies of these visceral afferent fibers are located in the dorsal root ganglia much as are those of somatic afferent fibers. The central processes derived from these cells enter the spinal cord in the dorsal roots.

Some visceral pain fibers enter the central nervous system as parasympathetic fibers, but the visceral regions so supplied are not extensive. Apparently the vagus nerve does not contain pain fibers below the origin of the recurrent laryngeal nerve. Pain impulses from the lower part of the alimentary canal and from the bladder are conducted into the central nervous system via the dorsal roots of the sacral nerves and therefore traverse parasympathetic afferent fibers.

Two kinds of visceral pain are recognized: referred and deep or unreferred.

Referred Visceral Pain. This component of visceral pain is referred to, and localized on, the surface of the body. Referred visceral pain is *dermatomal*, that is, it is referred to the *dermatome* supplied by the dorsal root through which the visceral pain impulses enter the spinal cord. A dermotome is a region of the skin which receives afferent innervation from a single dorsal spinal root. Dermatomes for man have been carefully mapped, but knowledge on this point for animals is meager.

That referred visceral pain is dermatomal is well established, but the explanation of the fact is somewhat in doubt. The *convergence-projection* theory fits well with modern knowledge of the physiology of the nervous system and is believed to afford an adequate explanation of referred visceral pain. Visceral afferent fibers and cutaneous pain fibers both converge on a nerve cell which gives origin to a fiber of the spinothalamic tract. Pain impulses from the viscera therefore reach the same area of the brain that pain impulses from the skin would reach. The sensation of pain is therefore projected to, and localized on, the part of the body surface that experience has shown to be the source of stimuli when a certain part of the brain is receiving impulses.

Hyperesthesia, or excessive sensitiveness of the skin, may accompany irritation of the viscera. This is dermatomal in reference.

Muscular rigidity may accompany irritation of the viscera. This occurs as a viscerosomatic reflex because of the connections in the spinal cord between the visceral afferent paths and the motoneurons. It is a flexor reflex, and in peritonitis, for example, rigidity of the abdominal muscles and the resulting immobilization would assist in localizing the infection.

Deep Visceral Pain. In visceral pain in man, and presumably in animals, there is a severe, deep, unreferred, poorly localized component. The explanation of the poor localization of this pain probably lies in the fact that the individual does not know from visual or other experience the source of the painful stimulation and therefore lacks the background of knowledge necessary for localization.

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PART VIII

The Special Senses

Chapter XXXVI

VISION

ANATOMICAL CONSIDERATIONS

THE eye may be said to comprise the eyeball or globe of the eye, the optic nerve, and certain accessory structures: the eyelids, conjunctiva, lacrimal apparatus, and ocular muscles. The eyeball is a spheroidal body consisting of three tunics or coats and containing the aqueous humor, crystalline lens, and vitreous humor (Fig. 151).

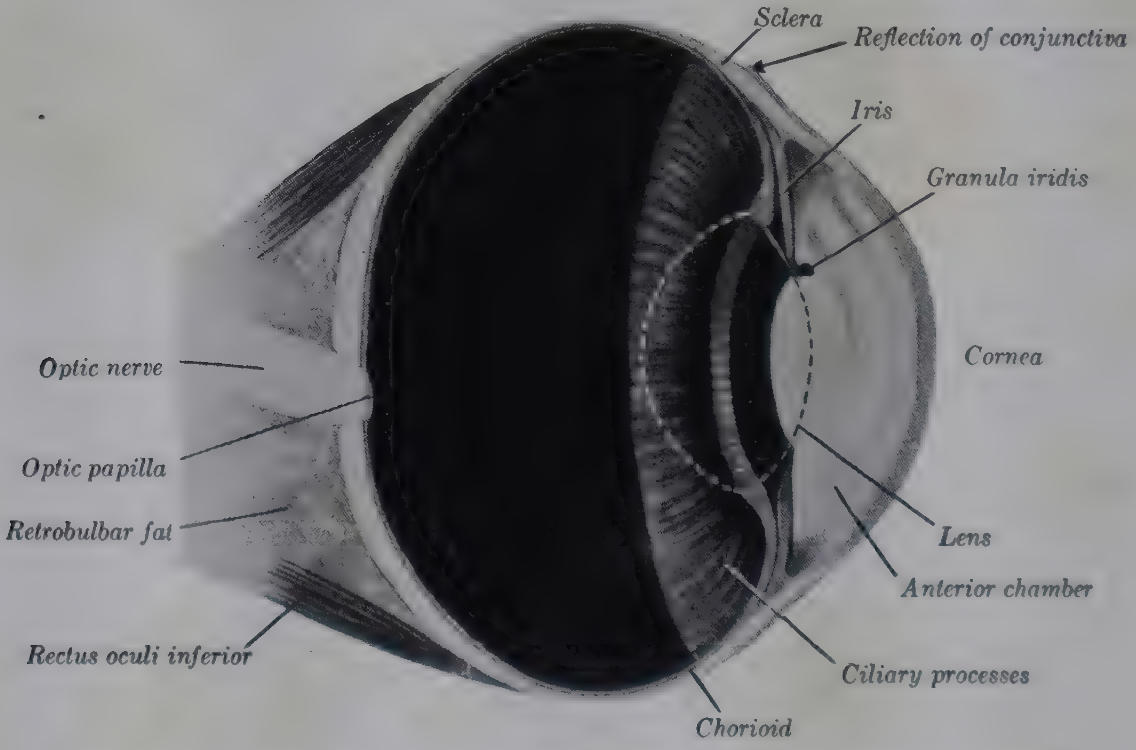
Sclera
Reflection of conjunctiva
Iris
Granula iridis
Cornea
Optic nerve
Optic papilla
Retrobulbar fat
Lens
Anterior chamber
Rectus oculi inferior
Ciliary processes
Chorioid

FIG. 151.—Vertical section of eyeball of horse. (From Sisson's *Anatomy*; copyright—W. B. Saunders Company.)

The Tunics of the Eye. The *fibrous tunic* or external coat gives strength to the eyeball. It consists of an anterior part, the cornea, and a posterior part, the sclera. The cornea is a transparent, colorless, nonvascular connective tissue structure with an index of refraction so nearly the same throughout that it is practically homogeneous optically, The sclera forms the greater part of the fibrous tunic. It joins the cornea at the sclerocorneal junction. It is composed largely of dense white fibrous connective tissue and is opaque to light.

The *vascular tunic* or middle coat comprises the choroid, the ciliary body, and the iris. The choroid consists mainly of blood vessels, pigment cells, and some connective tissue. Three layers are evident: the suprachoroid layer, whose cells contain a brownish pigment; the vascular layer or choroid proper, which contains the branches of the ciliary arteries and veins; and the capillary layer, which contains a rich capillary network. Between the vascular and capillary layers, in the posterior part of the eye, a peculiar, lustrous, opaque structure, the tapetum, is found. It occurs in all domestic animals except the pig. Its color varies greatly in different species and is often strikingly beautiful (Johnson). Light passing through the transparent retina is collected by the tapetum and reflected to the retinal receptors, thus providing more efficient stimulation. The chief function of the choroid is to supply nutrition to the outer layers of the retina.

The ciliary body is a ring of tissue joined to the choroid behind and to the iris in front. Its main components are the ciliary processes and the ciliary muscle. The numerous ciliary processes form a circle of radial folds surrounding the lens and giving attachment to its suspensory ligament. They are very vascular structures. The ciliary muscle is a ring of smooth-muscle fibers. Some of these are arranged meridionally and others circularly.

The iris is a muscular diaphragm arising from the ciliary body. It presents a central opening, the pupil, whose shape varies in different species and with different degrees of dilatation (Johnson). The iris presents three layers: an external epithelial layer; a middle, usually pigmented, fibrous layer; and an internal, pigmented, epithelial layer. The muscle fibers of the iris, smooth in type, are arranged in two ways. Some surround the pupil and constitute a sphincter pupillae; others are radially disposed in the iris and form a dilator pupillae.

The *retina* or nervous tunic is the light-sensitive coat of the eye. It is connected to the brain by the optic nerve, whose receptors are the rods and cones of the retina. Embryologically the retina is in fact a part of the brain and the optic nerve a cerebral tract. The structure of the retina will be considered later.

The Contents of the Eye. The *lens* is a biconvex transparent mass situated between the vitreous body and the iris. Its anterior surface is bathed by the aqueous humor and is in partial contact with the iris. Its posterior surface, more strongly curved than the anterior, fits into a depression in the front of the vitreous body. The lens, although apparently optically homogeneous, is not actually so, its refractive power increasing from the periphery to the center. This fact helps to correct for the optical defect known as spherical aberration. The lens is inclosed in an elastic, transparent membrane known as the capsule. Supporting the lens is its annular suspensory ligament, which extends from the ciliary processes to the capsule of the lens, where it is inserted on each side of the equator of the lens. The spaces between the fibers of the suspensory ligament communicate with one another and with the posterior chamber and are filled with aqueous humor. Posteriorly the suspensory ligament is intimately related to the hyaloid membrane of the vitreous body.

The *vitreous body* is a transparent, jellylike substance found in the cavity of the eye behind the lens. It is probably to be regarded as delicate, loose, gelatinous connective tissue. The vitreous body has a water content of about 98 per cent. In origin and composition the liquid of the vitreous body resembles aqueous humor.

The *aqueous humor* is a watery liquid found in the spaces between the lens and the cornea and in the interstices of the suspensory ligament. Aqueous humor resembles cerebrospinal fluid in composition. It is derived from the blood, mainly that in the capillaries of the ciliary processes, but the mechanism of its formation is not fully known. One view is that it is formed by ultrafiltration (dialyzation); another, that it is formed by a secretory process. Kinsey and co-workers have recently studied the rate of movement of water into and out of the eye, the rate of accumulation of electrolytes in the anterior chamber, and the mechanism of aqueous humor formation. These investigators believe that nonelectrolytes (urea, glucose, etc.), as well as water, enter the anterior chamber of the eye by diffusion and electrolytes by secretion.

By a process of diffusion aqueous humor supplies nutrition to the avascular lens and cornea. The chief method of removal of aqueous humor is by absorption into the vein known as the canal of Schlemm, which is situated close to the corneoscleral junction. The contents of the eye are under a certain amount of pressure known as the intraocular pressure, which is equal to about 25 mm. Hg. It gives firmness and evenness to the eyeball.

Further anatomical facts will be given in conjunction with the physiological discussions.

THE EYE AS AN IMAGE FORMER

The Adequate Stimulus. A sensation of light may be produced by various kinds of stimuli affecting the retina or the optic nerve. Pressure, electrical stimuli, or cutting may be effective, but the adequate stimulus is the action of light on the retina. The eye is therefore an exteroceptor, a distance receptor (teleceptor), and a radioceptor. Objectively, light consists of electromagnetic waves propagated through space. Subjectively, it is the sensation experienced when the optic nerve is stimulated. The velocity of all electromagnetic waves is 300,000 km. per second, but their wavelengths vary greatly. Some waves (electric waves, infra-red rays) are too long to stimulate the retina, while others (ultraviolet rays, X-rays) are too short. Those waves (visible light) capable of stimulating the retina of man vary from about 0.00072 mm. (limit of the red) to 0.0004 mm. (limit of the violet) in length. In terms of Ångström units these values are 7200 and 4000, this unit being 10^{-7} mm. Visible light therefore covers somewhat less than an octave of the spectrum. Experiments seem to show that the eyes of mammals respond to the same spectral limits as the eyes of man. Infra-red radiations raise the temperature of substances that absorb them; they are therefore sometimes referred to as the thermal part of the spectrum. Ultraviolet radiations cause chemical activity in substances that absorb them; they are therefore referred to as the actinic part of the spectrum. Visible-light radiations stimulate the retina; they are therefore termed the luminous part of the spectrum. These distinctions, however, are not sharp, for the three parts merge into and overlap one another.

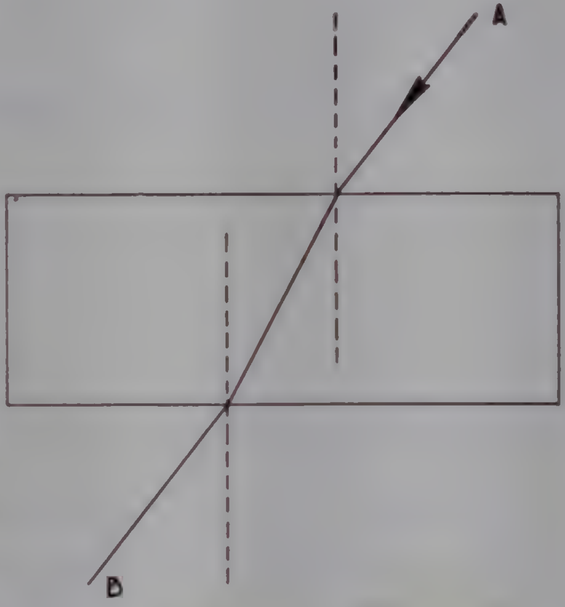

FIG. 152.—Showing the refraction of light. The rectangle represents a plate of glass surrounded by air. The dotted lines are normal (perpendicular) to the surfaces of the glass. AB represents an oblique ray of light. Upon passing from the rarer medium, air, to the denser medium, glass, the ray is refracted toward the normal, whereas upon passing from the denser medium to the rarer, the ray is refracted away from the normal.

Some objects, as the sun, an incandescent lamp, or a firefly, are visible by reason of light which they themselves give off. Most objects are visible by reason of light from other sources which they reflect to the eye.

All light rays diverge somewhat, but rays coming from a source not nearer than about 20 feet may, so far as the eye is concerned, be regarded as parallel.

Refraction. When light travels through a homogeneous transparent medium such as air, it moves at a uniform velocity and in a straight line; but when it falls obliquely on the surface of another transparent medium, part of it is reflected, while the rest travels through the new medium at a different velocity and in a different direction. This alteration in the direction and velocity of light is known as refraction. When light passes from a rarer medium into a denser, the direction of refraction is toward the normal (perpendicular), whereas when it passes from a denser medium into a rarer, the direction of refraction is away from the normal (Fig. 152). Light passing into a medium as a normal to its surface is not refracted. Because a denser medium bends and slows light passing into it from a rarer medium, the denser medium is said to have a greater index of refraction than the rarer.

The Convex Lens. When parallel rays of light fall upon the surface of a biconvex lens, they are converged to a focus or point beyond the other surface (Fig. 153). For parallel rays this point is known as the principal focus of the lens. The distance between the lens and the principal focus is known as the principal focal distance, or the focal length, of the lens. The focal length is determined by the curvature and the refractive index of the lens. The power, or "strength," of a lens is expressed by the reciprocal of its focal length. In physiological optics the unit of power of a lens is the diopter (D), which is a lens with a focal length of 1 meter. A lens with a focal length of 0.5 meter has a power of 2 D; one with a focal length of 2 meters, a power of 0.5 D, etc.

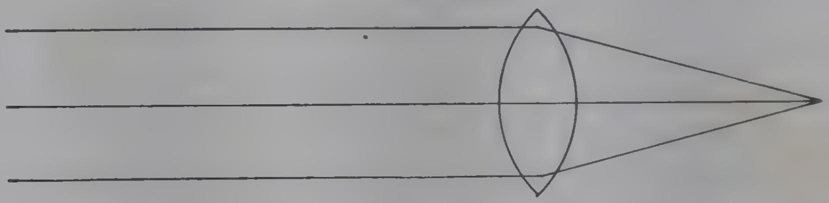
Fig. 153.—Showing the convergence of parallel rays to a point, the principal focus, after they have been refracted by a convex lens.

Conversely, if a luminous point is situated at the principal focus of a lens, the rays leaving the other surface of the lens will be parallel.

If a luminous point is situated at a distance from a lens greater than its focal length but not so great as to emit parallel rays, the rays, which are divergent, will be brought to a focus, on the other side of the lens, farther away than the principal focus. This is the conjugate focus (Fig. 154).

A line passing through the centers of curvature of the surfaces of a lens is known as the optic axis. Situated on this axis is a point, known as the nodal point, through which a ray of light may pass without undergoing refraction.

Image Formation. If light from an object is made to fall on a convex lens and a screen is placed at the correct distance behind the lens, an inverted image of the object is thrown on the screen. The photographic camera may be used to illustrate the formation of an image by a convex lens. If the camera is properly focused, an inverted image of the light-emitting object can be seen on the ground glass at the back of the camera. The eye acts like a convex lens or a photographic camera in the formation of an image. If the excised eyeball of an animal, especially an albino, is held near a candle, an inverted image of the flame can be seen on the retina. Although the image thrown on the retina is inverted, human beings, and, without doubt, animals also, see the object erect. This ability is acquired early in life.

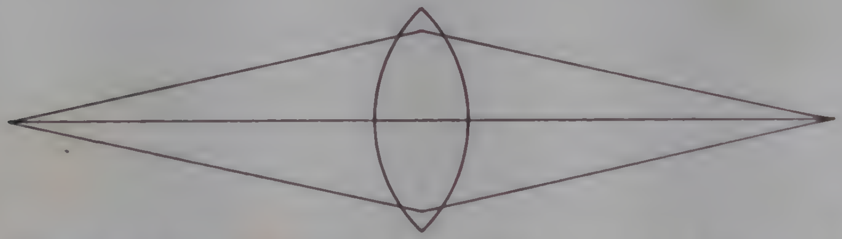

FIG. 154.—Showing the convergence of divergent rays to a point, the conjugate focus, after they have been refracted by a convex lens.

In the eye the principal refractive media are the cornea and lens. In the human eye the cornea is more refractive than the lens, whereas in the eyes of most mammals the reverse is true.

As in the photographic camera, so in the eye, the exclusion of light is important. In the eye the opacity of the sclera and the pigment of the choroid, retina, and iris ordinarily insure the exclusion of all light except that entering through the pupil. In albinos these pigments are absent and vision is poor.

Like other optical instruments, the eye shows several optical defects. One of these, *spherical aberration*, results from the fact that rays falling on the peripheral parts of a lens are refracted more than those falling on the central parts. Consequently the peripheral rays are focused sooner than the central, and a blurred image results. Spherical aberration is made negligible in the eye principally because the iris, acting like the diaphragm in a photographic camera, cuts off peripherally directed rays. The increase in refractive power of the lens of the eye from the periphery to the center (p. 668) also helps to compensate for spherical aberration. Another optical defect is *chromatic aberration.* This results from the fact that the short waves at the violet end of the spectrum are refracted more, and therefore brought to a focus sooner, than the longer red waves. The image therefore tends to have a colored outline. Although the eye possesses little compensation for chromatic aberration, the condition is ordinarily not noticeable. One reason why chromatic aberration is of little significance in vision is that those parts of the spectrum that are most important in chromatic aberration—extreme red and extreme blue—play only a minor part in stimulating the retina.

Accommodation. When the refractive mechanisms of the normal eye are in a condition of rest, parallel rays, that is, rays from objects not nearer than about 20 feet, are brought to a focus on the retina. Such an eye is said to be emmetropic (Fig. 155). Its posterior principal focus is located on the retina and its *far point* of distinct vision is at infinity (20 feet or more). Objects closer than 20 feet to the eye give off divergent rays, which are brought to a focus back of the retina. If such an object is to be seen distinctly, some adjustment in the optical system of the eye must take place. If the object is brought still closer to the eye, a point is finally reached beyond which further adjustment is impossible. This is the *near point* of distinct vision. Objects situated closer to the eye than this point cannot be seen distinctly.

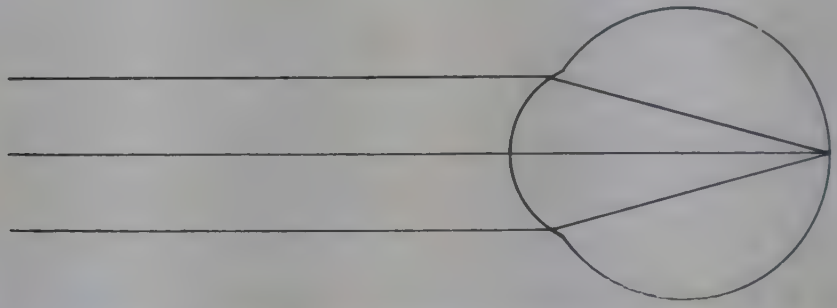

FIG. 155.—Emmetropia. Parallel rays are brought to a focus on the retina.

The adjustment in the optical system of the eye that makes possible the changes from distant vision to near vision, and the reverse, is known as accommodation, which may be compared with the focusing of a camera. The camera is focused for near objects by moving the screen farther back or by moving the lens farther forward. Accommodation in fishes is effected by moving the lens forward or backward; in some birds, by changing the curvature of the cornea. In man there is much evidence that accommodation for near objects is brought about by increasing the curvature of the lens, mainly the anterior surface, by the action of the ciliary muscles. Essentially the same process probably holds good for most mammals. However, in domestic animals, particularly Herbivora, the power of accommodation is weak and the ciliary muscle is poorly developed. The fibers of the ciliary muscle are so arranged that when they contract, the anterior part of the choroid is drawn forward and the apices of the ciliary processes are pulled together. Thus tension on the suspensory ligament is relaxed, and the lens, which is somewhat flattened by the pull exerted on it by the suspensory ligament, bulges, principally forward, where the resistance is less. The vitreous body prevents any extensive change in the curvature of the posterior surface of the lens. Relaxation of the ciliary muscle allows the structures passively to assume their former position.

With increasing years there is a gradual decrease in the elasticity of the lens and therefore in the power of accommodation. In old age (man) the power of accommodation is lost, and glasses become necessary for close work. The condition is designated as presbyopia.

The ciliary muscle receives motor innervation from the third cranial nerve, the fibers belonging to the parasympathetic division of the autonomic nervous system. They arise in the motor nucleus of the third nerve as preganglionic fibers and make synaptic junctions with nerve cells in the ciliary ganglion, from which postganglionic fibers arise. These fibers are paralyzed by atropine and stimulated by pilocarpine, arecoline, acetylcholine, and eserine.

Work by Olmsted and Morgan shows that the cervical sympathetic is also concerned in accommodation. Stimulation of the cranial end of the nerve results in flattening of the anterior surface of the lens.

Accompanying accommodation for near objects there are associated muscular movements: the pupil contracts, thus improving vision, and the eyes, in animals possessing stereoscopic vision, converge on the object examined.

Pupillary Changes. The fact that the pupil contracts during accommodation was noted above. Furthermore, the size of the pupil changes in response to the amount of light entering the eye. This is a familiar fact and can easily be demonstrated. In the dark the pupil dilates because of the contraction of the dilator muscle, whereas in the light it is constricted because of contraction of the sphincter muscle.

The reactions of the pupils to light are reflexes. In Amphibia, birds, and some of the lower mammals (rabbit) the reflex contraction of the pupil occurs only in the eye stimulated. In man and the higher mammals the reflex is bilateral (Harris). Ungulata seem to occupy an intermediate position, the contraction in the unstimulated eye being slight. The afferent fibers for the pupillary reflex are contained in the optic nerve, but it is uncertain whether they are identical with the ordinary sensory fibers of this nerve. The efferent fibers belong to the parasympathetic and sympathetic divisions of the autonomic nervous system. The parasympathetic fibers, contained in the third cranial nerve, supply motor innervation to the sphincter muscle of the pupil. Their cell relays are located in the ciliary ganglion. The reflex center is situated in the midbrain. The sympathetic fibers supply motor innervation to the dilator muscle. The fibers leave the spinal cord in the ventral roots of the last cervical and first two thoracic nerves and pass in the sympathetic chain to the anterior cervical ganglion, where they terminate. From nerve cells in this ganglion postganglionic fibers arise and run to the dilator muscle. The action of these nervous mechanisms is tonic, but the principal reflex regulation is brought about through the parasympathetic innervation.

The pupillary nervous mechanism is influenced by many drugs. Atropine paralyzes the constrictor nerves and causes the pupil to dilate. Pilocarpine, arecoline, acetylcholine, and eserine augment the constrictor effects and cause the pupil to contract. Adrenaline stimulates the dilator nerves and causes pupillary dilatation.

The pupillary responses to light, drugs, and accommodation are not as well defined in Ungulata as in other mammals (Johnson).

Errors of Refraction. When the mechanisms of accommodation are at rest the emmetropic eye brings parallel rays to a focus on the retina. However, all eyes are not emmetropic, many suffering from various errors or defects of refraction. When the resting eye brings parallel rays to a focus in front of the retina, the condition is known as myopia, short-sight, or near-sight (Fig. 156). A blurred image results. The most common cause of the condition is an abnormally long anteroposterior diameter of the eye. It may be caused, however, by too refractive an optical apparatus. In either case the result is the same. In myopia both the far point and the near point of distinct vision are located closer to the eye than in emmetropia. Myopia can be corrected by the use of a concave lens, which decreases the refractive power of the eye.

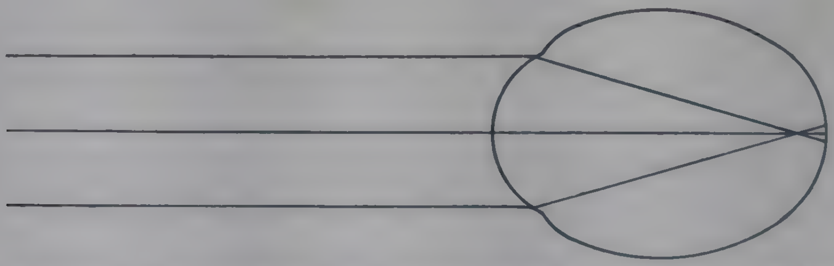

Fig. 156.—Myopia. Parallel rays are brought to a focus in front of the retina.

When the resting eye brings parallel rays to a focus behind the retina, the error of refraction is known as hypermetropia, hyperopia, or far-sight (Fig. 157). The most frequent cause of hyperopia is a shortened condition of the eyeball. In order to see anything clearly the hyperope must accommodate. The defect can be corrected by the use of a convex lens, which causes the rays to come to a focus sooner.

Another common error of refraction is known as astigmatism. It is present when the refractive surfaces of the eye are not segments of spheres, that is, when they have different radii of curvature in different meridians. Therefore rays of light reaching the meridians of unequal curvature are not focused to a common point, and poor vision results. It is as if the eye were emmetropic in some meridians and myopic or hyeropic in others. Astigmatism may affect the cornea or the lens, or both, but the cornea is more commonly at fault. If the defect lies in a vertical or horizontal plane, it can be corrected by the use of a cylindrical lens—a lens that refracts in one plane but not in the other.

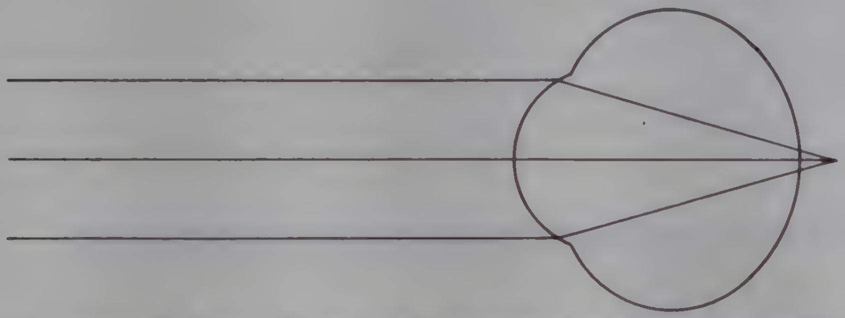

FIG. 157.—Hyperopia. Parallel rays are brought to a focus behind the retina.

Myopia with or without astigmatism is, according to Smith, the chief visual defect in horses. However, the amount of error is not great. Johnson states that myopia with or without astigmatism occurs frequently in domestic animals; other errors of refraction are met with. Most wild mammals have hyperopic vision.

THE RETINA[*]

The retina is a nervous structure showing the presence of four kinds of neurons: the rod and cone visual cells, neurons of the first order; bipolar cells, neurons of the second order; the ganglion cells, neurons of the third order, giving origin to the fibers of the optic nerve; and horizontally running correlation neurons (Fig. 158). The axons of the ganglion cells, that is, the fibers of the optic nerve, are the only ones that pass beyond the retina itself. The initial parts of the rod and cone visual cells constitute the rods and cones proper. They lie next the pigment layer, which is the outer retinal layer. The rods and cones are the light-sensitive elements of the retina. The optical apparatus of the eye, considered above, serves to throw an image on these structures, whereupon nerve impulses are set up, which pass, by way of the visual path (p. 642), to the brain.

That the rods and cones are the ultimate receptors is indicated by a number of facts such as the following: (1) The retinal blood vessels and corpuscles form shadows which may be seen under certain conditions. Evidently the receptors in the retinal wall are external to the blood vessels; otherwise the shadows would not fall on them. (2) Rods and cones are absent from the place in the retina where the optic nerve leaves the eyeball. This area, the optic disk, is composed only of nerve

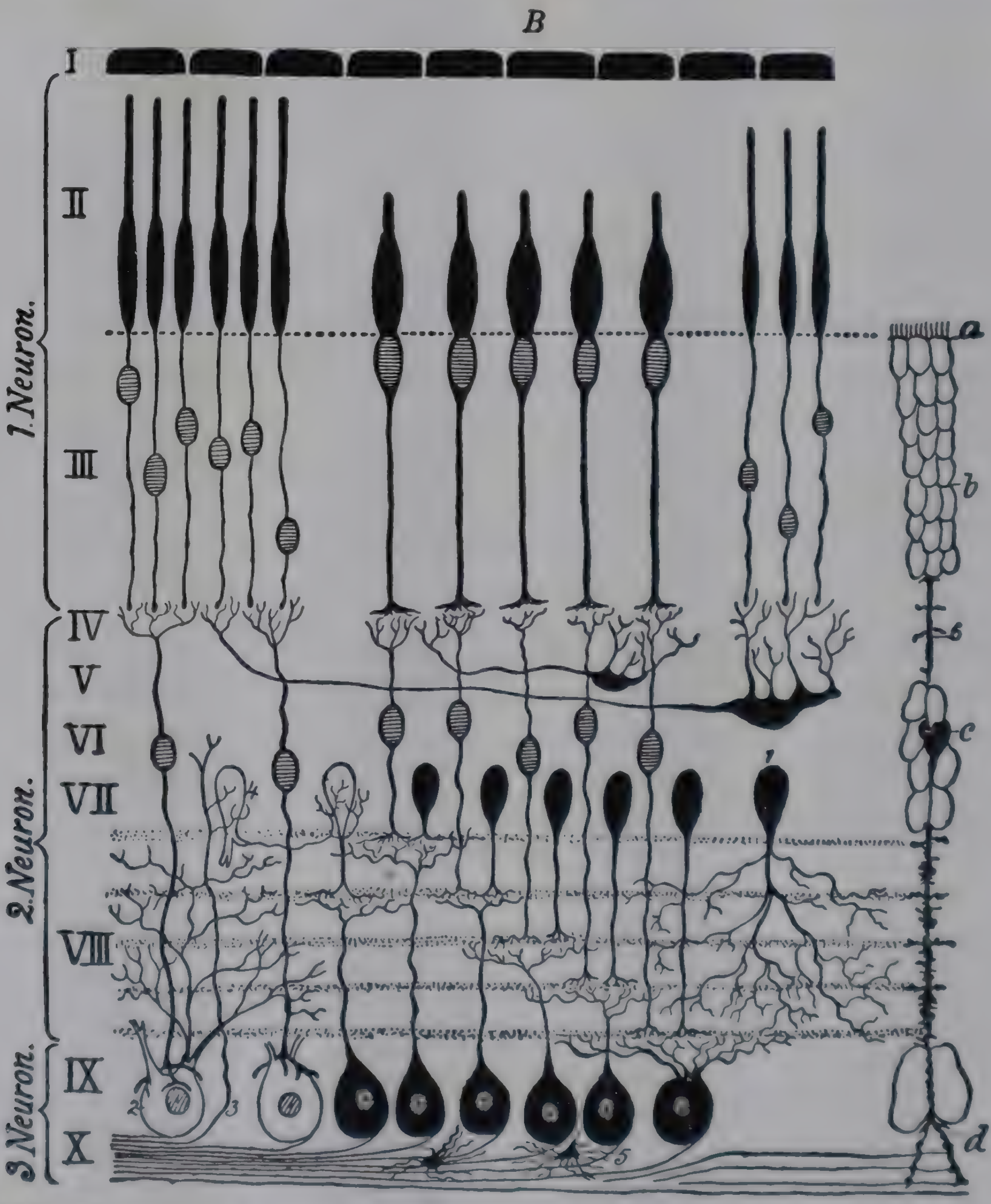

FIG. 158.—Schematic diagram of the structure of the retina. I, Pigment layer; II, III, rod and cone visual cells (the rods and cones proper are shown in solid black above the dotted line); V, horizontally running correlation neurons; VI, bipolar cells; IX, ganglion cells; X, axons of the ganglion cells, going to form the optic nerve. (Greef; from Howell's *Physiology*; copyright—W. B. Saunders Company.)

fibers. It is insensitive to light and is called the blindspot. Since the optic disk is composed of nerve fibers, it follows that these elements are insensitive to light. (3) The retina of man and the anthropoid apes shows the presence of an area, the yellow spot or macula lutea, toward the center of which is a depression, the fovea centralis. The fovea is so situated that it is on the line of sight, or visual axis. Composed mainly of cones, it is the retinal point of most acute vision. Mammals below man and anthropoids (felines may be an exception) do not possess a true fovea centralis but do have a less sharply delimited area that is more sensitive than the rest of the retina.

Objective Changes in the Retina. When light acts on the retina certain changes take place, resulting in stimulation of the rods and cones. A nerve impulse is then set up, which passes to the visual area in the brain, where the sensation is perceived. Several changes in the retina have been demonstrated to occur, but it is not certain that any of these represents the fundamental change that causes the nerve impulse to be generated.

Electrical Changes. That the eye is the seat of electrical changes has been shown by many workers. If an excised eye is connected with a galvanometer by means of nonpolarizable electrodes, one on the cut optic nerve and the other on the cornea, the usual injury potential is obtained. When this is compensated for, potential changes actually due to illumination of the eye may be studied. It is found that both light and darkness give characteristic electrical responses. Another interesting observation is that all frequencies from red to violet give the same general type of response. The place of origin of these photoelectric changes is probably the retina itself. Their full significance is not known. They are in some way related to, or associated with, excitation of the receptors.

Visual Purple. Occurring in the outer segments of the rods of all vertebrates is an unstable reddish pigment known as visual purple or rhodopsin. If present in the cones, it occurs only in very small amounts. This substance decomposes and bleaches in the light but regenerates in the dark. When it was first discovered it was thought that a comprehensive photochemical theory of vision might be built around visual purple; but its virtual absence from cones, which apparently are the receptors in bright-light vision, indicates that it cannot be concerned in all aspects of vision. Its presence in rods—which are believed to be the receptors in dim-light vision—and the fact that it regenerates in darkness indicate that it is concerned in vision under low intensities of illumination. A similiar pigment, visual violet, has been demonstrated in cones. For the relation of vitamin A to the photochemical changes occurring in the retina, see p. 521.

The Duplicity Theory. An eye that has been exposed to bright light for some time is said to be light-adapted. Vision by the light-adapted eye is designated as photopic vision. An eye that has been protected from light for a considerable interval is said to be dark-adapted. Vision by the dark-adapted eye is designated as scotopic. According to the duplicity theory, vision by the dark-adapted eye is carried out through the mediation of the rods, whereas vision by the light-adapted eye is carried out through the mediation of the cones. This would mean that night vision or vision under low intensities of illumination, in which color phenomena are absent, is a function of the rods; whereas day vision or vision under high intensities of illumination, including color vision, is a function of the cones. In support of the duplicity theory the following facts may be enumerated: (1) The region of keenest photopic vision is the fovea centralis (man and anthropoids), which zone is practically rod-free. (2) The region of best scotopic vision (man) is not the fovea, or central part of the retina, but the peripheral part. This explains why it is possible to see a star brighter, not by looking directly at it, but by turning the gaze slightly away. (3) Total color-blindness is apparently due to functional failure of the cones; night-blindness, to functional failure of the rods. (4) Certain nocturnal animals (cats) and birds (owls) have retinas in which rods predominate; diurnal birds (pigeons) show a preponderance of cones.

Color Vision. When light of a certain wavelength acts on the retina, certain receptors are stimulated, nerve impulses pass to the cerebral cortex, and the sensation of a certain color is perceived. White light is a mixture of waves of various lengths. Some objects reflect all light and are white; others reflect no light and are black. Still other objects, absorbing certain wavelengths and scattering others, are colored, the color depending on the wavelengths scattered.

Each color possesses the following qualities: hue, such as red, yellow, green; degree of saturation or purity, which depends on the amount of white mixed with the color; and luminosity, or brightness. Colors agreeing in these respects are said to be identical.

The colors of the spectrum—red, orange, yellow, green, blue, violet—are termed simple colors. If an arrangement is made whereby two or more colored spectral rays can be thrown simultaneously on the same retinal spot, sensations of mixed colors result. Two kinds of mixed colors are distinguished: those that are not represented in the spectrum, for example, purple; and those that are.

A sensation of white may be produced by the simultaneous action of certain pairs of colors on the same retinal spot. Such pairs are said to be complementary colors. The following pairs of spectral colors are complementary: red and greenish blue, orange and cyanic blue, yellow and indigo blue, greenish yellow and violet.

It has been shown experimentally that the color sensation resulting from all possible lights or light mixtures can be matched by the color sensation resulting from the mixture of suitable amounts of a few colors, three being the minimum number. The best three colors are red, green, and blue. Normal color vision is therefore said to be trichromatic.

A detailed consideration of color vision is beyond the scope of this book. Discussions and references may be found elsewhere (Parsons, Helmholtz, Roaf).

Color Vision in Animals. It is evidently difficult to determine to what extent color preception is present in animals. Experiments have not always yielded clear-cut results. The general belief is that color perception is poorly developed or absent in most mammals. However, color perception is possessed by birds, at least by some species.

DIVERGENCE OF THE OPTIC AXES

The optic axis is a line passing through the centers of the refracting surfaces of the eye. The size of the angle formed by the optic axes and the median line has been measured in many species. The angle varies greatly, there being a close relation between certain life habits of the species and the amount of the divergence of the optic axes from the midline. In man and the anthropoids, which possess well-developed binocular vision, the axes are practically parallel to the median line. In animals that use their eyes to search for prey (felines), the angle is small. In animals that depend largely on vision for protection (rodents, ungulates), the angle is large. Following are some of Johnson's figures indicating the size of the angle formed by the optic axes and the median line: cat, 7 to 9; dog, 15 to 20; pig, 33; wild sheep, 50; ox, 52; giraffe, 72; common hare, 85 degrees.

PERISCOPIC, BINOCULAR, AND STEREOSCOPIC VISION

Closely related to the divergence of the optic axes of animals are the facts of periscopic, binocular, and stereoscopic vision. *Periscopic vision* is seen in animals with eyes laterally placed and often possessing movements independent of each other. Evidently such vision is monocular, it being impossible for both eyes to view the same object at the same time. Many birds, as parrots, pigeons, chickens, ducks, and swans, and some mammals, as rabbits and hares, have periscopic vision.

Binocular vision is vision in which both eyes view the same object simultaneously. For binocular vision to be possible, it is necessary that the eyes should be so placed in the head that the fields of vision overlap to some extent, or that the animal should possess the power of converging the eyes, or both. Rodents, having laterally placed eyes, possess little or no power of binocular vision. Ungulates, with eyes somewhat more anteriorly situated, are a little better off. Rodents have no power of convergence and ungulates only slight power. Birds of prey, carnivorous mammals, especially felines, and primates have the best-developed binocular vision. In flesh-feeders it is associated with accuracy of movement in seizing prey; in primates it is associated with skilled movements of the anterior extremities.

Stereoscopic vision is that form of vision in which the three dimensions of space are clearly perceived. It is best developed in primates, although felines, which have optic axes that diverge only slightly, probably possess fairly good stereoscopic vision. For an animal to have stereoscopic vision in the sense that it is possessed by man, it is essential that it have good binocular vision, but more than this is required. It is necessary that the optic nerve fibers decussate incompletely at the chiasma, and that the eyes be so constructed that the image will fall on corresponding points in the two retinas. Decussation of the fibers of the optic nerve is complete in the lower mammals but not in the higher. There are a few direct (nondecussating) fibers in the rabbit and horse. In the cat and dog there are more, and in primates, especially man, there are many. The areas in the two eyes that constitute corresponding points are the foveae, as seen in primates, and apparently similiar sensitive areas as seen in some other mammals. Corresponding points are probably in functional connection with the same nerve cells in the visual portion of the cortex. It is probable that animals below the primates possess a kind of stereoscopic vision different from that possessed by primates or dependent on differences in the cortical responses.

Chapter XXXVII

HEARING, SMELL, AND TASTE

HEARING

THE ear is made up of three divisions: the external ear, consisting of the pinna or auricle and the external acoustic meatus; the middle ear, consisting of the tympanic cavity, with its contents, and the Eustachian tube, with its diverticulum, the guttural pouch (Equidae); and the internal ear or labyrinth, consisting of an acoustic part, the cochlea, and a nonacoustic part, the vestibular organ. The functional significance of the vestibular organ is considered elsewhere (p. 625). The cochlea, supplied by the cochlear branch of the acoustic nerve, contains the receptors for the sense of hearing. The essential function of the external ear is to receive sound waves; of the middle ear, to modify them and to facilitate their passage to the perilymph of the internal ear and thus to the sound receptors in the cochlea. The principal structures of the ear are shown schematically in Fig. 159.

The Auricle. The function of this structure is to collect sound waves, which are then transmitted to the tympanic membrane by way of the external acoustic meatus. The mobility of the auricle, as seen in most mammals, enhances its value as a collector of sound waves by enabling it to be turned in the direction of the sound.

The Tympanic Membrane. Completely separating the external acoustic meatus from the tympanic cavity, or cavity of the middle ear, is a thin septum known as the tympanic membrane. It is composed of three layers: the external layer is continuous with the skin lining the external acoustic meatus; the middle layer is composed of radially and circularly arranged connective tissue fibers; the internal layer is continuous with the mucous membrane of the tympanic cavity. Attached to the internal surface of the membrane is the manubrium, or handle, of the malleus, the first of the auditory ossicles. Vibrations of the tympanic membrane are in this way transmitted to the chain of bones and so to the perilymph. An important feature of the tympanic membrane is that it is aperiodic, that is, has no inherent period of vibration, and therefore can transmit any frequency without modifying it.

The Auditory Ossicles. These are three small bones, the malleus, incus, and stapes, found in the tympanic cavity. They comprise a chain extending from the tympanic membrane to the fenestra ovalis. Through them the vibrations of the tympanic membrane are transmitted to the perilymph of the labyrinth. The malleus, the first bone in the chain, is, as noted above, attached to the tympanic membrane by means of the manubrium. The head of the malleus articulates with the head of the incus. Several ligaments help to hold the malleus in place. The incus presents a head, which articulates with the head of the malleus, and two processes. A ligament attaches the shorter process to the wall of the tympanic cavity. The long process articulates with the head of the stapes. The foot-plate of the stapes is inserted into the oval window, to whose margins it is attached by a membrane. In transmitting the vibrations of the tympanic membrane to the perilymph, the auditory ossicles act as a bent lever. Since the manubrium of the malleus is longer than the long process of the incus, it is evident that the vibrations of the tympanic membrane are transmitted to the perilymph with increased force but with decreased amplitude.

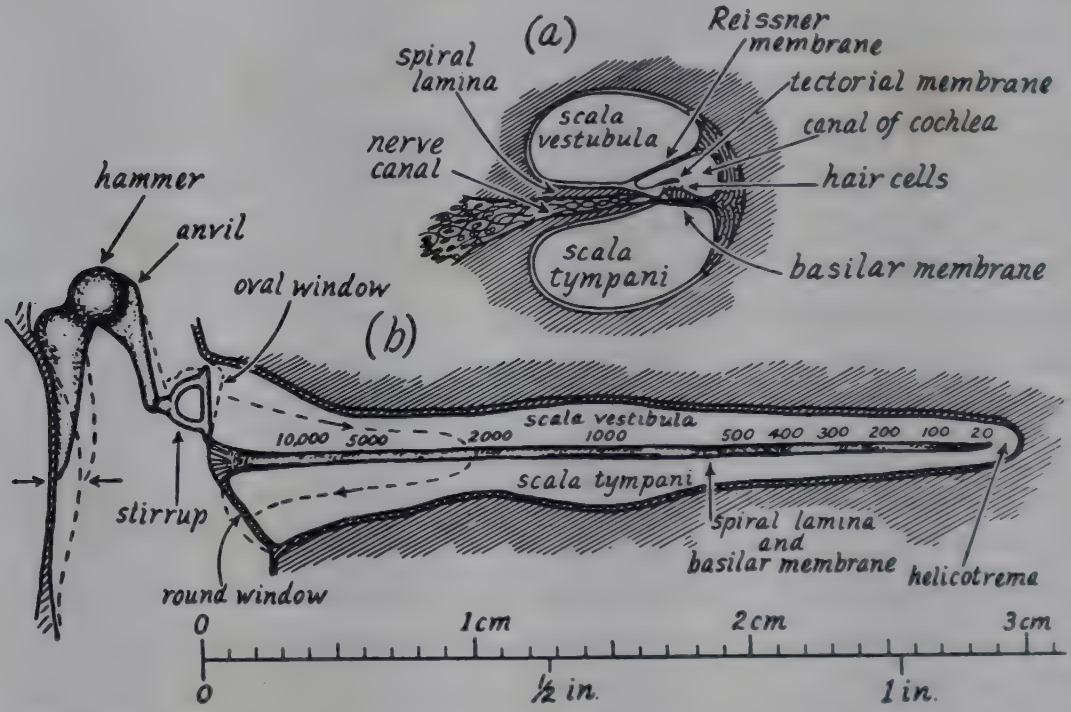
(a)
spiral lamina
Reissner membrane
tectorial membrane
canal of cochlea
nerve canal
scala vestubula
hair cells
scala tympani
basilar membrane
hammer
anvil
oval window
(b)
scala vestibula
10,000
5000
2000
1000
500
400
300
200
100
20
scala tympani
stirrup
spiral lamina and basilar membrane
helicotrema
round window
0
1cm
2cm
3cm
0
½ in.
1 in.

FIG. 159.—The cochlea: (*a*) cross-section (Reissner membrane is the same as the vestibular membrane); (*b*) represented as if uncoiled to illustrate the different regions of the basilar membrane sensitive to sounds of different frequencies. (From White's *Classical and Modern Physics,* D. Van Nostrand Company, Inc.)

The Eustachian Tube and Guttural Pouch. Connecting the tympanic cavity with the pharynx is the Eustachian tube, whose presence insures that the air pressure in the tympanic cavity shall be the same as that on the outside of the body. Ordinarily closed, at least in man, the pharyngeal aperture of the tube is opened during swallowing. Therefore, should an inequality of atmospheric pressure on the two sides of the tympanic membrane result, it can quickly be corrected by deglutition.

The guttural pouch, found among domestic animals only in Equidae, is a remarkable diverticulum of the Eustachian tube. Sisson states that the average capacity of each pouch in the horse is about 300 cc. The function of the guttural pouch is not known. A number of hypotheses have been proposed (see Fish) but all lack experimental support and most of them are otherwise deficient. Experiments by Fish show that in the horse air enters the guttural pouch through the relaxed aperture of the Eustachian tube during expiration and leaves mainly during the expiratory pause; during inspiration the aperture of the Eustachian tube is closed. The significance of this movement of air into and out of the pouch during respiration is not clear.

The Stimulus. The ear, like the eye, is a distance receptor. Before considering the mechanism of hearing, it will be profitable to review briefly the physical nature of sound waves, which constitute the adequate stimulus of the cochlear receptors. Sound waves are vibratory disturbances in physical media. The sound waves that affect higher animals are transmitted in air, although water and many solids are also capable of transmitting such waves. When a body surrounded by air is thrown into vibration, the adjacent air molecules are made to vibrate, or move to and fro, thus producing alternating phases of compression and rarefaction. Then the air adjacent to this agitated region is also affected, and so on, the disturbance traveling outward from the vibrating body, in three dimensions, in the form of a wave. The speed of sound waves in air varies somewhat depending on the temperature, the average at ordinary temperatures being about 1100 feet per second.

Physically, sounds differ as to frequency, intensity, and wave form. Frequency refers to the number of vibrations per second, and is perceived as *pitch*. The intensity of a sound wave depends on both the frequency and amplitude of the vibration. Intensity determines the *loudness* of the sound. Wave form refers to the presence or absence of overtones, which determine subjectively the *quality*, or *timbre*, of a sound. Thus although a violin string and a piano string may be vibrating at the same intensity and frequency, it is possible to distinguish between the sounds emitted. The difference between the sounds lies in their quality or timbre, which is determined by the overtones.

The Cochlea. The acoustic labyrinth or cochlea contains the receptors for the sense of hearing. It consists essentially of a spiral bony tube, wound several times around a bony supporting pillar (modiolus), and a much smaller tube, known as the cochlear duct, contained within the bony tube. Inside the cochlear duct is found the organ of Corti with its sensory hair-cells and the terminations of the cochlear nerve (Fig. 160). The cells of origin of the cochlear nerve fibers are bipolar nerve cells situated in the spiral ganglion. The latter is located in the modiolus. The peripheral branches of these nerve cells end in relation to the hair-cells of the organ of Corti. The central branches end in the ventral and dorsal cochlear nuclei of the pons.

The cochlear duct, somewhat triangular in cross-section, begins in the vestibule and extends the length of the bony canal, to whose walls its base and apex are attached. Forming one side of the cochlear duct and separating its cavity from that of the scala vestibuli is the delicate vestibular membrane. Forming the other side of the duct and separating its cavity from that of the scala tympani is the much firmer basilar membrane. Situated on the inner side of the basilar membrane and running its entire length is the highly specialized organ of Corti. The basilar membrane is composed of a large number of fibers whose length increases and whose tension apparently decreases from the base to the apex of the cochlea. This membrane is believed to be the structure that receives the sound waves in the perilymph and thus

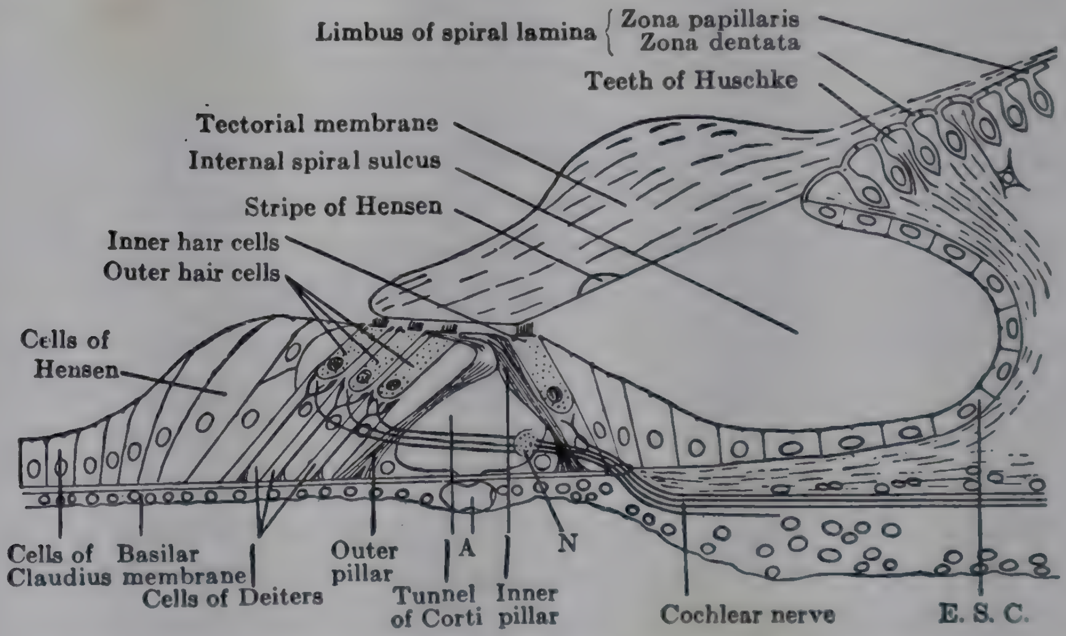
Limbus of spiral lamina { Zona papillaris
Zona dentata
Teeth of Huschke
Tectorial membrane
Internal spiral sulcus
Stripe of Hensen
Inner hair cells
Outer hair cells
Cells of Hensen
Cells of Claudius
Basilar membrane
Cells of Deiters
Outer pillar
A
Tunnel of Corti
Inner pillar
N
Cochlear nerve
E. S. C.

FIG. 160.—Diagrammatic cross-section of the organ of Corti. (From Herrick's *Neurology;* copyright—W. B. Saunders Company.)

causes stimulation of the hair-cells and their associated nerve endings in the organ of Corti.

The cochlear duct, filled with endolymph, communicates with the saccule through the canalis reuniens. The scala vestibuli and the scala tympani, filled with perilymph, communicate with each other at the apex of the cochlea, the helicotrema. At the base of the cochlea the scala vestibuli communicates with the vestibule. The scala tympani ends at the fenestra rotunda, which is closed by a membrane, the secondary tympanic membrane. By its elasticity this membrane compensates for pressure changes in the perilymph as a result of the impact delivered to the latter by the stapes at the fenestra ovalis. This, however, may not represent its sole function.

The Organ of Corti. This very complex sensory epithelial structure, extending from the beginning to the end of the cochlear duct, rests upon the basilar membrane. It is composed of supporting cells of several kinds, sensory epithelial cells known as the auditory hair-cells, the tectorial membrane, and the fibers of the cochlear nerve. The hair-cells are the structures by which sound waves are converted into nerve impulses. The free ends of these cells possess stiff cilia, while the basal ends are related to the terminal fibrils of the cochlear nerve. It is estimated that there are more than 20,000 hair-cells in the organ of Corti and about as many fibers in the cochlear nerve. The cilia of the hair-cells project, near its free margin, into the tectorial membrane, a gelatinous pad covering the outer surface of the organ of Corti. At its other margin this membrane is attached to the wall of the cochlea at the spiral lamina.

The Mechanism of Hearing. Sound waves entering the external acoustic meatus throw the tympanic membrane in vibration. The waves so generated are transmitted mechanically across the tympanic cavity by the action of the auditory ossicles. The movements of the foot-plate of the stapes set up waves in the perilymph of the labyrinth, which cause the basilar membrane—less likely, the tectorial membrane—to vibrate. These fine movements cause changes of pressure on the cilia of the hair-cells, probably by bending them, and so on the nerve terminations at the bases of the cells. Nerve impulses thus aroused are transmitted to the central nervous system. Some of the impulses stimulate auditory reflex centers in the brain-stem and others reach the auditory center in the cerebral cortex.

The cochlea shows potential changes, known as the microphonic effect, which *may* be concerned in stimulating the nerve fibers. The potential changes result from pressure variations caused by the sound waves and are probably piezo-electric effects. They should not be confused with the spike potentials shown by the nerve fibers.

Just how the basilar membrane behaves in response to waves in the perilymph is not known. A theory of hearing having much in its favor is the resonance theory, which holds that the basilar membrane is a resonator whose different parts respond by sympathetic vibration to sound waves in the perilymph. Different frequencies cause vibrations in the membrane at different levels, thus stimulating different nerve fibers. Low frequencies cause sympathetic vibrations in the parts of the membrane at the apex of the cochlea, where its fibers are longest, apparently slackest, and most heavily loaded by the columns of liquid in the cochlear duct. High frequencies, on the contrary, cause vibrations in the basal parts of the membrane, where conditions opposite to those just mentioned prevail. If the sound is compound, that is, composed of several frequencies, each frequency causes sympathetic vibration in that part of the membrane which is in tune with it. Perception of intensity, or loudness, of sound depends largely upon the frequency of the nerve impulses generated in the cochlear nerve fibers. A loud sound causes a sympathetic response of greater amplitude in the fibers of the basilar membrane and so calls forth impulses of a higher frequency in the nerve fibers by the action of the hair-cells. An extension of the resonance theory is the resonance-volley theory, which is discussed in a review of the physiology of hearing by Wever.

The Range of Hearing. The range of frequencies through which sound can be perceived varies in different species. In man, in whom the determinations are attended with less difficulty than in animals, the average pitch limits are 20 and 20,000 vibrations or cycles per second (Fletcher). There is little doubt that some animals can perceive frequencies much higher than 20,000 cycles per second. By the method of conditioned reflexes, Pavlov appears to have demonstrated that the upper pitch limit of the dog is about 100,000 cycles. The silent dog whistle emits frequencies too high for man to hear but below the upper pitch limit for dogs. The frequency most audible to the rat appears to be 40,000 cycles (Gould and Morgan). Frequencies as high as 98,000 cycles cause potential changes in the cochlea of bats. Studies of the range of hearing in birds have been made by Brand and Kellogg.

Location of Sound. Ability to judge the direction from which sound is coming is dependent largely on the fact that sound is heard louder and sooner in the ear nearer the source. Movements of the pinnae must greatly assist animals in locating the source, the sound being heard loudest and earliest when the pinna points in the direction from which it is coming. In man movements of the head in listening serve a similiar purpose.

SMELL

The Receptors. The mucous membrane of the nasal cavity presents two regions, a limited olfactory region in the upper part of the cavity and a much larger respiratory region lining the rest of the cavity. The size of the olfactory region in different species varies directly with the degree of development of the sense of smell. The epithelium of the olfactory region of all vertebrates shows the presence of at least three kinds of cells, basal, sustentacular or supporting, and olfactory. The last-named are bipolar nerve cells whose central processes become the fibers of the olfactory nerve and whose peripheral processes extend to the surface of the olfactory epithelium. On this surface, covered with mucus, each peripheral process terminates in a number of delicate filaments, the olfactory hairs.

The Stimulus. The adequate stimulus of the receptors in the olfactory region is minute odorous particles usually brought in with the inspired air. Some of this air gradually reaches the olfactory region and causes slight olfactory stimulation. Then follows sniffing, which causes rapid changes of air in contact with the olfactory mucous membrane and thus strong stimulation. However, not all particles stimulating the olfactory organ reach it by way of the anterior nares. Foods during mastication give off odorous particles which reach the olfactory organ by way of the posterior nares.

Although the odorous particles reaching the olfactory mucous membrane are in a gaseous state, there is reason to believe that they must become dissolved before acting as stimuli. Parker points out that the olfactory hairs, the ultimate receptors, are probably always submerged in watery mucus. Therefore in order for the odorous particles to reach the hairs, the particles must become dissolved in this liquid. Then follows some sort of chemical reaction between the dissolved material and the receptor, whereupon a nerve impulse is started.

The amount of odorous material just sufficient to cause olfactory stimulation varies with different substances. In all cases it is very small, and in the case of strongly odorous subtances it is inconceivably small. A number of substances are known to give off odorous particles for a considerable time without undergoing any demonstrable loss in weight. Following are some figures derived from tests (man) made to determine the smallest concentration of the substance in the air necessary for olfaction; the figures are given in micrograms of substance per liter of air: camphor, 5; ether, 1; citral, 0.5 to 0.1; cumarin, 0.05 to 0.01; vanillin, 0.005 to 0.0005.

Efforts have been made to classify odors on the basis of the subjective sensations aroused, but the very numerous sensations have not yet been brought into a satisfactory classification. There is some evidence that the odor of a substance is related to its chemical constitution.

Olfaction in Animals. It is a well-known fact that many animals have a much keener sense of smell than man has. The dominant position occupied by the olfactory sense in these keen-scented animals is indicated by the great development of their olfactory apparatus, peripheral and central. Such animals are designated as macrosmatic. Most of the domestic animals belong to this group. Animals in which the olfactory apparatus is poorly developed are designated as microsmatic. Man, monkeys, and some aquatic mammals belong to this group. There is a third group, including a number of aquatic mammals, in which olfaction is apparently absent. They are said to be anosmatic.

According to Negus the *epiglottis* plays an important role in olfaction in many animals by forming with the soft palate a partition that prevents the breathing of air by the mouth. During eating, and at other times when the mouth is open, air is thus made to flow through the nasal passages, and in this way keen olfaction is attained. This arrangement is best seen in macrosmatic animals and among domestic animals is well exemplified in the horse.

The most important function of the olfactory sense in animals is to aid them in the search for food. In a less important way olfaction is related to the sexual life of the animal and to the protective reactions. Especially in man olfaction is related to the reflex secretion of the digestive juices.

The *vomeronasal organ*, found in some form in all mammals, is believed to be closely related to the olfactory sense (Parker, Read).

TASTE

The Receptors. The peripheral gustatory organs are the taste-buds of the oral cavity. Although found principally on the dorsal surface of the tongue, their distribution is not limited to this region. They are also found on the epiglottis, the soft palate, the posterior wall of the pharynx, and elsewhere. The number is greater in young individuals than in mature. The taste-buds on the tongue nearly always occur in association with the vallate, foliate, and fungiform papillae. The other papillae seldom show them. Taste-buds occurring on a vallate papilla of a pig are illustrated in Fig. 161.

Taste-buds are composed of taste-cells, which are found in various stages of growth. The peripheral end of the taste-cell presents a terminal filament, the taste-hair, with which may be regarded as the point at which the dissolved stimulating substance comes in contact with the taste-cell. The gustatory nerve fibers end in intimate relation with the taste-buds or their constituent cells, although protoplasmic continuity between them does not exist. Nevertheless the relation is so close that degeneration of gustatory nerve fibers results in the disappearance of their associated taste-buds.

Separate gustatory nerves do not exist, the fibers of taste being contained in several of the cranial nerves. The glossopharyngeal nerve supplies taste sensation to the posterior third of the tongue, the facial to the anterior two-thirds, and the vagus to the epiglottis and perhaps other nearby structures.

The Stimulus and the Sensations. The adequate stimulus for the taste receptors is an aqueous solution of a great number of materials. Any substance that is not water-soluble is without taste. During mastication solid and semisolid foods are mixed with saliva, which dissolves some of their soluble constituents. These solutions penetrate the pores of the taste-buds, come in contact with the taste-hairs, and cause some sort of chemical change whereby the gustatory nerve fibers are stimulated.

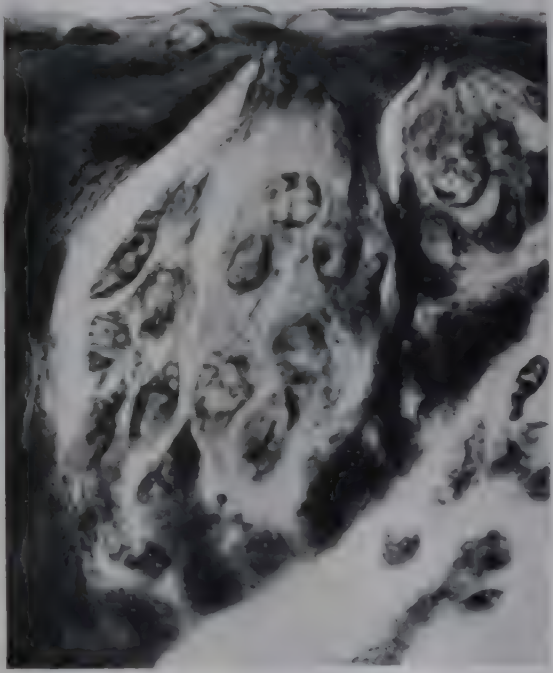

FIG. 161.—Section of a vallate papilla of a pig to show two taste-buds. (Courtesy of Dr. Margaret Sloss.)

Experimental analysis in man indicates that all taste sensations fall into a few well-defined classes. This is in contrast with the apparently unlimited number of olfactory sensations, which so far have defied satisfactory classification. All true tastes apparently belong to one of four classes: sour, saline, bitter, and sweet. Some workers claim that there are other true tastes, as metallic and alkaline, but others maintain that these tastes are mixtures of several sensations. With the exception of sour, saline, bitter, and sweet, the numerous sensations aroused during eating are undoubtedly due in the main to stimulation of the receptors of olfaction, touch, warmth, cold, and the common chemical sense.

The *sour taste* is in some way related to the hydrogen ions yielded by the acid substance in solution, but hydrogen ion concentration and sourness do not always run parallel. This is especially true of some organic acids: solutions of acetic acid taste more sour than would be expected upon the basis of hydrogen ion concentration. In man the sour taste is acutest at the lateral margins of the tongue.

The *salty taste* is well exemplified by sodium chloride, although it is given by many other salts. The work of a number of investigators indicates that the anion of the dissolved salt is the stimulus. In man the salty taste is best developed on the tip and edge of the tongue.

The *bitter taste* is given typically by practically all alkaloids, but a number of substances of diverse chemical constitution (ether, the glucosides, magnesium sulfate, etc.) are also bitter. In man the bitter taste is most distinct at the base of the tongue.

The *sweet taste* is given by many organic compounds, of which the carbohydrates are characteristic. Moreover, a number of salts, for example, lead acetate, have a sweet taste. It is at present impossible to relate the sweet taste to chemical constitution. In human beings the sweet taste is most evident at the tip of the tongue.

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PART IX

The Endocrine Organs, Reproduction, and Growth

Chapter XXXVIII

THE ENDOCRINE ORGANS

THE endocrine organs are those structures whose specific metabolic products are discharged directly, and possibly indirectly by way of the lymph, into the blood, by which they are transported to their places of action. These organs are frequently referred to as endocrine glands and sometimes as ductless glands, and the term internal secretion has long been used to designate the process by which the specific products of the organs in question are formed. These specific products are sometimes referred to as chemical messengers or regulators since they travel by way of the blood stream. This method of control or co-ordination in the body may be contrasted with the nervous method. Chemical regulation is the slower, apparently more primitive type; nervous regulation is the more efficient type and is probably a more recent phylogenetic acquisition of the organism.

A chemical regulator[1] produced by an endocrine organ has long been designated a hormone, which term literally means "to stir up." The word hormone was adopted in the belief that all such chemical regulators excite function in other organs. As a matter of fact, it is now known that some chemical regulators inhibit function, and the term hormone is used to cover both the excitatory and the inhibitory principles.

Endocrine organs may be divided into two groups: those that are only endocrine in function, namely, the thyroid, parathyroids, pituitary, adrenals, pineal, and possibly the thymus; and those that not only produce hormones but other substances as well, namely, the pancreas, testicle, ovary, gastric epithelium, and intestinal epithelium. In this chapter the physiology of the strictly endocrine organs will be studied. The hormones of the gastric and intestinal linings and the pancreas are dealt with in Chapters XIII and XV, respectively. The hormones of the sex glands are considered in Chapters XXXIX and XL.

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[1] The subject of chemical regulation is a broad and important one. Not all chemical regulators are produced by endocrine organs; for example, carbon dioxide, concerned in the regulation of respiration and of other physiological activities, is a universal product of cellular metabolism.

The pituitary gland occupies a unique position in the endocrine system since its anterior lobe produces a series of hormones which act upon and control the activity of certain other endocrine glands. It is, therefore, to a large extent, the means by which a general endocrine regulation is effected.

THE THYROID

The thyroid, found throughout the vertebrate phylum, shows a uniform origin and development in all species (Marine). In mammals it consists of two lobes, one on each side of the trachea close to its junction with the larynx. In most animals the lobes are connected by an isthmus crossing the ventral surface of the trachea. However, in some animals (dog, cat) the isthmus usually disappears in embryonic life; but this statement may not apply in regions in which goiter is widespread.

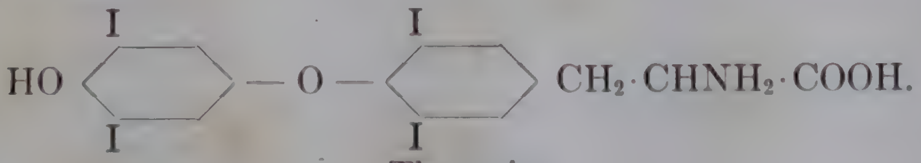
Structure. The thyroid is made up of numerous closed follicles, usually spherical. Their microscopic appearance is similar in all animals from fish to man (Marine). They are lined with a single layer of low cuboidal epithelial cells, and are filled with a viscid substance which has long been known as colloid. The colloid contains, combined with a protein, the specific thyroid hormone, *thyroxine*. The blood supply of the thyroid is very rich; few organs receive a more abundant supply. The efferent nerve supply is entirely autonomic, the preganglionic fibers leaving the spinal cord between the second and seventh thoracic segments. The peripheral relays are located in the middle and anterior cervical ganglia. Vasomotor nerves to the glands are abundant; but it is doubtful if secretory nerves exist, for transplanted thyroids function normally. It is believed that the rate of secretion is varied by alterations in the blood supply. The anterior pituitary also has an effect through the thyrotrophic hormone which stimulates the thyroid.

Effects of Removal. The results of early studies on the effects of removal of the thyroid (thyroidectomy) were badly clouded because of the simultaneous removal of the parathyroids. It is now recognized that the two organs are separate structures physiologically and must be so regarded in extirpation experiments. The manifestation that always follows thyroidectomy, regardless of age or species, is a decided lowering of metabolism as indicated by measurements of the heat production or gaseous exchange. Gross external manifestations vary with the age of the animal. In young animals of all species there is stunting of physical, mental, and sexual development, the animals remaining in an infantile condition. In mature animals, especially herbivores, clinical symptoms may be slight and confined to dryness and thickening of the skin, falling of the hair, and physical and mental sluggishness; or they may be practically absent (Simpson—sheep; Houssay and Hug—horse).

All the changes just mentioned are believed to be dependent upon the suspension of the essential function of the thyroid: that of maintaining, through its hormone thyroxine, a higher rate of metabolism than would otherwise exist, and that of providing, through variations in the output of thyroxine, a means of altering the metabolic rate to meet the changing requirements of the organism. Just how thyroxine produces this effect on metabolism is not known; it may act as a catalyzer. The metabolic rate of isolated tissues of animals previously fed with thyroid substance is higher than normal, and tissues from thyroidectomized animals show a metabolic rate lower than normal.

It has been found that feeding thyroid or thyroid extracts compensates in every way for the loss of the gland.

The Thyroid Hormone. The secretion of the thyroid contains the hormone thyroxine, which has been isolated, analyzed, and synthesized (Harington; Harington and Barger). It may be considered therefore that so far as the chemistry of the hormone itself is concerned our knowledge is remarkably complete. The structural formula of the hormone is:



Thyroxine

The compound is thus seen to be related to the amino acid tyrosine, which is probably its precursor. The viscid protein—thyroglobulin—present in the vesicles of the thyroid contains thyroxine.

In addition to thyroxine, the thyroid contains the compound diiodotyrosine. This substance, itself physiologically inactive, is believed to be an intermediary compound in the synthesis of thyroxine.

The Secretion of the Hormone. The thyroid cells produce a thyroxine-containing secretion, which is removed from the gland mainly by the blood, but apparently to some extent also by the lymph. Whether the secretion is discharged directly into the circulation or is passed first into the follicles to be removed later is not known. Some workers believe that it is ordinarily discharged directly into the circulation and is passed into the follicles only when it is secreted in excess of body needs. Another view, based on recent work, is that in the normal gland the secretion passes first into the follicles, whereas in exophthalmic goiter it passes directly into the blood.

The Relation of Iodine to the Thyroid. The thyroid has a special affinity for iodine. Marine has shown that nearly a fifth of a single dose of 38 mg. of potassium iodide given to a dog by the mouth may be stored in the gland within two hours. The average amount of iodine in the normal thyroid of animals has been shown by Marine and co-workers to vary in different species from 2.2 to 3.5 mg. per gram of dried gland. These workers have demonstrated further, in many species, that there exists an intimate relation between the amount of iodine in the thyroid and its histological appearance. The iodine content was found to vary directly with the amount of stainable colloid and inversely with the degree of hyperplasia of the gland. In general, when the iodine content exceeded 0.1 per cent of the dried weight of the thyroid, no hyperplasia was found. Recent studies, in which iodine labeled by being rendered radioactive was injected into the blood stream, show that it appears in the thyroid three minutes after it is injected and that a large proportion is absorbed within ten minutes (Hertz and co-workers).

Fenger as well as Seidell and Fenger made studies of the iodine content of the thyroids of cattle, hogs, and sheep, special attention being paid to seasonal variations. It was found that there are two to three times as much iodine present in the organs in the months between June and November as in the months between December and May. External temperature appears to be the most important factor determining the fluctuations. Enlargement of the organs in the winter is one factor in causing a (relative) decrease in the iodine content while increased secretion to maintain body temperature is another.

Disturbances of Thyroid Function. Since much of what is known about thyroid function has been derived from studies of clinical cases, a few words on the pathological physiology of the thyroid are in order. The diseases associated with disturbances of thyroid function may be classified as follows, though the question of the classification of thyroid diseases is most controversial.

Hypothyroidism, Myxedema
    (a) Simple goiter
    (b) Colloid goiter
    (c) Cretinism

Hyperthyroidism
- (a) Exophthalmic goiter
- (b) Malignant tumors of the thyroid

Hypothyroidism (Fig. 162) usually arises as the result of a deficiency of iodine in the food and water. It appears in widespread areas of the globe, in the Swiss Alps, portions of the Balkan Peninsula, and in restricted areas of Scandinavia, Spain, and England. In Asia it is prevalent in the region of the Himalayas; in South and Central America it is prevalent in the Andes and Cordillera regions. In the United States it is prevalent in the Great Lakes region and in the upper Mississippi Valley, but it is also found in the Pacific Northwest and in restricted areas in Virginia, West Virginia, Pennsylvania, and Missouri (Fig. 163). In Canada it is found in British Columbia and in Quebec. All these areas have one thing in common, a deficiency of iodine in the soil. Some believe, as these are nearly all limestone regions, that an excess of lime is a contributory factor. The condition can be almost entirely prevented by the addition of iodine to the food or drinking water. Simple goiter, with or without enlargement of the gland, and colloid goiter, with enlargement, may appear at any age. They are charac-

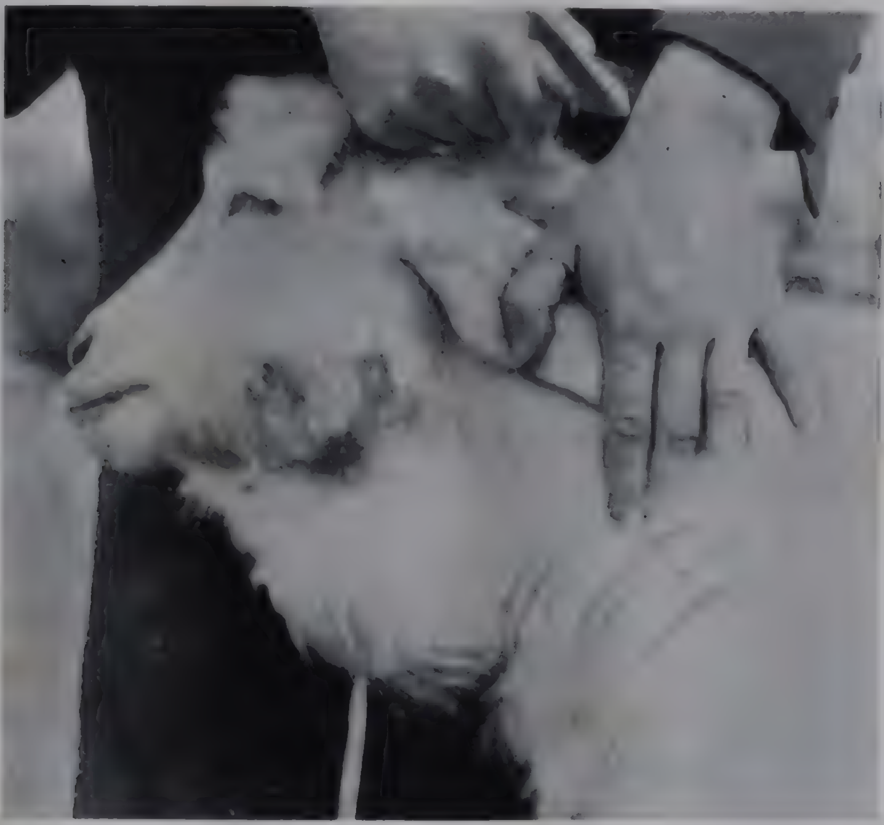


FIG. 162.—Hypothyroidism: a well-developed simple goiter. (Courtesy of Dr. J. W. Kalkus.)

terized by a lowered metabolism, mental sluggishness, lack of muscle tone, a type of obesity in which the subcutaneous tissues are edematous, the shedding of hair, and impaired fertility in both sexes. Growth is also greatly retarded. The syndrome is similar to that found after total or subtotal extirpation of the gland. In colloid goiter the gland attempts to compensate by overgrowth, while in simple goiter the active tissue is replaced by inactive tissue. If the female is bred, abortions are frequent and the young which are born are often cretinous.

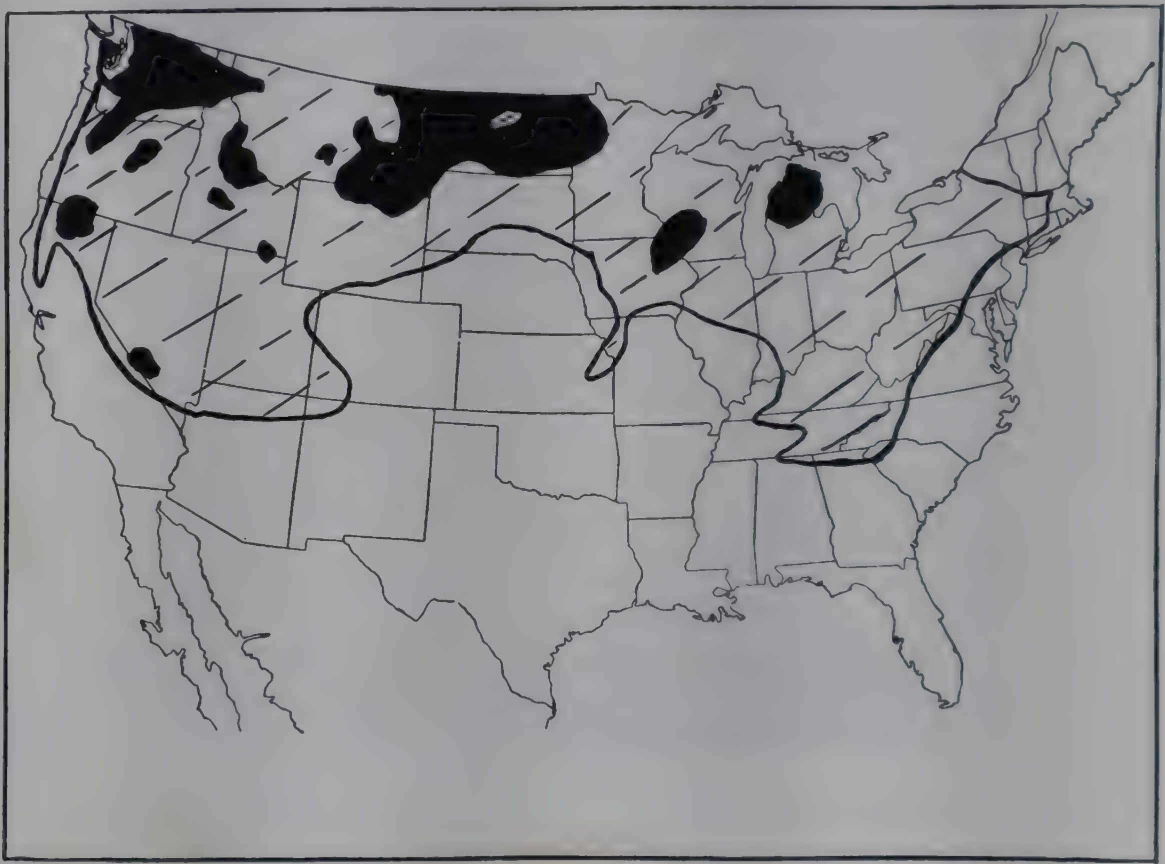


FIG. 163.—Iodine deficiency in livestock and in man in the United States. The dark areas are approximately the regions in which goiter in livestock is found. The striped area north of the thick line is the additional area in which goiter has been reported in man. (Human data redrawn from McClendon, *Iodine and the Incidence of Goiter,* University of Minnesota Press, 1939.)

Cretinism appears when the mother has insufficient iodine in her food. Clinically it is similar to infantile myxedema but the thyroid fails to develop. It cannot be relieved by the addition of iodine, as the gland cannot synthesize thyroxine. Continuous administration of the hormone is necessary to remedy the condition, but its appearance can be prevented by feeding iodine to the pregnant mother.

Hyperthyroidism is due to an overfunctioning of the gland. Probably this is caused in most cases by an oversecretion of the thyrotrophic hormone of the anterior pituitary. The metabolic rate is high; the subject is mentally unstable and restless, and becomes prematurely senile. The eyes often protrude from their sockets. The condition may be relieved by the operative removal of some of the thyroid tissue or by the action of ingested radioactive iodine. Exophthalmic goiter is not known to occur clinically in animals.

Thyroprotein. Reineke and Turner have recently produced iodinized proteins by a simple chemical process. These contain thyroxine and their administration in the feed to lactating animals has increased the milk yield by as much as 20 per cent. This effect is due to a general stimulation of metabolism. The heart beat and the respiratory rate, as well as the milk yield, rise when these substances are fed. It is not yet known how valuable this method of increasing the milk yield may prove to be as there is some question whether the yield can be maintained at a higher level over a long period, and whether the increased metabolic rate may cause the cows to wear out prematurely.

These workers have also experimented with the drugs thiourea and thiouracil, which depress the activity of the thyroid gland. The claim is made that this condition, which lowers the metabolic rate, causes the animals to fatten more readily. It is premature yet to decide whether the method has a place in agriculture, but pigs fed thiouracil after they have reached 150 lb. in weight gain more rapidly than their litter-mate controls. The conformation of younger pigs fed thiouracil differs markedly from that of normal pigs of the same age; the hams, especially, are more developed.

Interrelations. The subject of functional interrelations among the endocrine organs is very complicated and in many cases controversial. However, considerable progress has been made in this field in recent years, especially with respect to the interrelations of the hormones of the anterior pituitary.

Thyroid–thymus. See p. 712.

Thyroid–adrenals. Injection of thyroid extract increases the response of the animal to adrenaline injection. The assumption is that the thyroid hormone raises the irritability of the structures acted upon by adrenaline. Both thyroxine and adrenaline are related to tyrosine; both hormones can increase the heat production of the organism. These facts suggest interrelations.

Thyroid–pituitary. The anterior lobe of the pituitary produces a thyrotrophic hormone which provides a normal stimulus to thyroid activity. The hormone acts directly on the thyroid cells and not on the thyroid nerves, for transplanted thyroids and surviving thyroid cells in vitro are stimulated as well as the thyroid in its normal location.

Likewise the thyroid secretion influences the production of the thyrotrophic hormone. An increase in thyroid activity reduces the production of the thyrotrophic hormone, whereas a decrease causes more to be produced. Thus a balance between the production of the two hormones is maintained.

Thyroid–sex-glands. That the thyroid gland enlarges during puberty, pregnancy, and the menopause has long been known; and removal of the sex glands causes some effect on the thyroid, usually a slow involution. These and other facts indicate an interrelation, but its nature is as yet uncertain. It is probable that the interrelations of the thyroid and the gonads involve the anterior pituitary.

Thyroid–mammary-glands. The level of milk secretion is related to the degree of thyroid activity. Several workers have shown that the milk yield may be increased to some extent by the administration of thyroxine while thyroidectomy decreases the yield, and there is some evidence that the thyroids of dairy cattle are more active than those of beef cattle (Reece and Turner).

THE PARATHYROIDS

The parathyroids, present in amphibians, reptiles, birds, and mammals, are believed to have essentially the same function in all animals. Usually there are two pairs of parathyroids. Marked variations in the position of the glands are seen in the different species, and, indeed, the position varies somewhat in animals of the same species. The upper pair is more closely related anatomically to the thyroid than is the lower pair. Accessory parathyroids may be present in the thorax imbedded in the thymus, and along the course of the carotid artery in the cervical and upper mediastinal regions. The parathyroids are very small, the four of them weighing, in some species, less than half a gram. Each gland is composed of epithelial cells, which may be clumped compactly together, arranged in strands, or grouped in lobules. The lobules or follicles, when present, may contain colloid although this bears no relation to thyroid colloid. The iodine content of the parathyroids is no greater than that of tissues generally. The blood supply of the parathyroids is rich. Their scant nerve supply is believed to be mainly, if not entirely, vasomotor. That the parathyroids may function in the absence of nervous connection is indicated by transplantation experiments.

Effects of Removal. The parathyroids have been removed experimentally from animals of many species, and while the symptoms following extirpation vary considerably, it is believed that the underlying metabolic change is the same in all animals, the differences being due to minor causes. Seen most strikingly in the dog, the characteristic manifestation of parathyroidectomy is the development of the symptom-complex known as parathyroid tetany (Fig. 164). This appears during a period varying usually from 12 hours to 3 or 4 days after the operation. It is characterized by hyperexcitability of the peripheral nerves and by muscular tremors, spasms, and convulsions. The milder muscular symptoms are believed to be due to increased irritability of the spinal cord, whereas the convulsions arise from higher levels of the nervous system. Cats, tending to become depressed from the start, do not show as well-defined tetany as dogs. Monkeys show milder symptoms than dogs and usually develop chronic tetany. Lambs may show acute tetany, although loss of the thyroid and parathyroids is tolerated better and for a longer time in herbivores (rabbits may be an exception) than in carnivores (Simpson). According to Larson and Elkourie, goats fail to show tetany following the usual operation for the removal of the thyroid and the parathyroids, but definite muscular tremors are seen in some cases. To what extent this failure of goats to develop tetany was due to the presence of accessory parathyroid tissue is not definitely known, although no such tissue could be found at autopsy. Other experiments on parathyroid removal in goats have shown more definite neuromuscular symptoms.

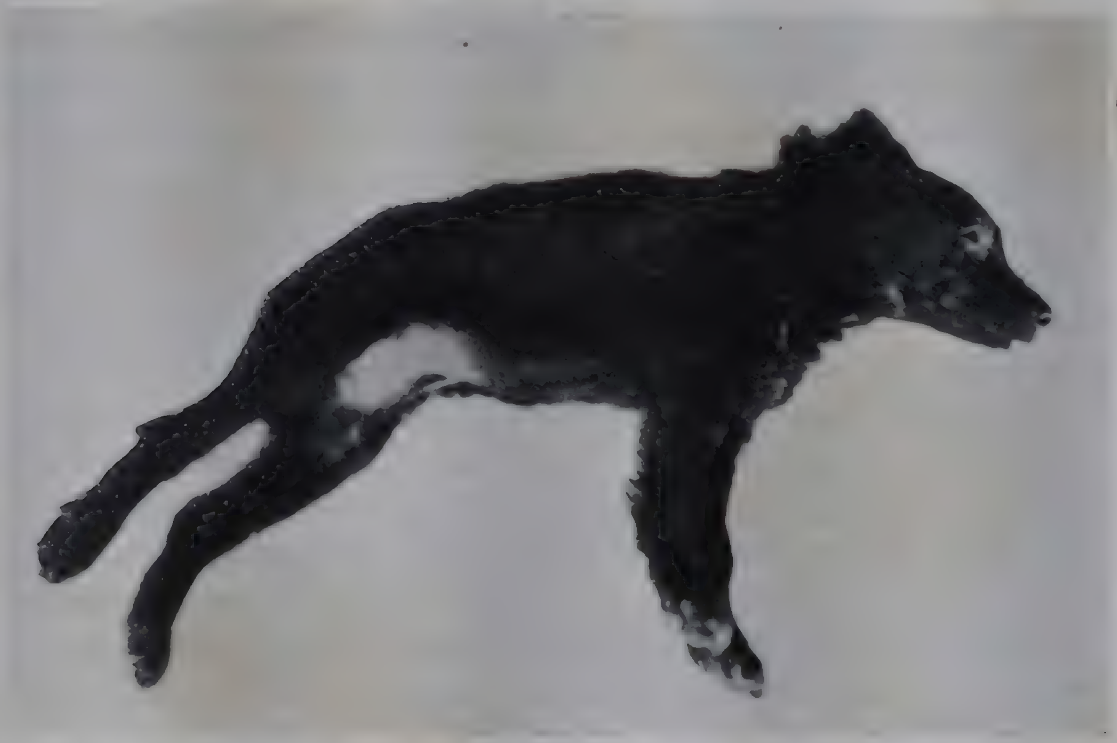


FIG. 164.—Parathyroid tetany in a thyroparathyroidectomized dog. (From Collip, *Journal of Biological Chemistry,* 1925, 63.)

As regards the necessity of the parathyroids for life, it is probable that a sudden destruction or removal of all parathyroid tissue will bring about changes leading to a fatal termination in most species (Dragstedt). However, owing to the difficulty of removing all parathyroid tissue, with the possibility that some of it may remain, extirpation experiments have given different results in different species and in animals of the same species. In dogs removal of the four glands is fatal in nearly 100 per cent of the cases; in cats only in 50 to 80 per cent of the cases. In rabbits tetany develops earlier and is more rapidly fatal than in dogs or cats. In rats parathyroidectomy is rarely fatal. Age is an important factor, young animals manifesting a much more violent and rapidly fatal form of tetany than mature animals.

Changes in the Blood Following Parathyroidectomy. The most characteristic blood change in parathyroid tetany is a lowered calcium content. The concentration of calcium is lowered from the normal of 10 to 12 mg. per 100 cc. of serum to 8 to 5 mg. per 100 cc. An accompanying increase in the inorganic phosphorus is often noted. Other blood changes have been reported, but in most cases the findings have not been confirmed. Phosphorus excretion is reduced.

The work of Dragstedt and his collaborators and of others indicates that parathyroidectomized dogs may be kept alive indefinitely by means other than specific parathyroid therapy, for example, by calcium feeding. After several weeks the treatment may be stopped without the return of tetany. These findings have not escaped criticism. Marine believes that calcium therapy simply tides the animals over until accessory parathryroid tissue develops and adjustment to, or compensation for, low blood calcium takes place. According to this view, such animals would be regarded as being in a state of latent tetany.

The Parathyroid Hormone and Its Action. The work of Collip and his collaborators has yielded a preparation containing the active principle or hormone of the parathyroids. The extract is made by acid hydrolysis of the parathyroids of the ox. The composition of the hormone has not been determined, but it is protein in nature, possibly a polypeptide. The action of the hormone is to cause an increase in the calcium content of the blood. It raises the serum calcium level of parathyroidectomized dogs to normal and that of well dogs to a point above normal. It may be given orally, subcutaneously, or intravenously. A close parallelism is noted between the clinical condition of parathyroidectomized dogs and the blood calcium level. As the latter rises to normal, the condition of the dogs improves and becomes normal. The term *parathormone* is usually used for the parathyroid hormone.

The effect of parathyroid extracts on normal calves has been studied by Robinson, Huffman, and Burt, who found that although the calves responded similarly to dogs, they were apparently less sensitive to the extract than were dogs. The serum calcium could be raised to as much as 18 mg. per 100 cc. in 30 hours. The visible manifestations of overdosage were drowsiness and bloating. Continued injection resulted in death. The extra calcium present in the blood as a result of injection of the hormone comes from the calcium stores in the bones.

The prevailing view of the action of parathormone, not entirely without question, is that it primarily regulates the excretion of phosphorus by the kidneys. As phosphorus and calcium metabolism are closely related, a disturbance in the metabolism of the former directly affects the level of the latter in the blood. Since calcium excess or deficiency produces more obvious clinical symptoms than a disturbance in the phosphorus level, calcium changes attract more attention. When the calcium level is lowered by withdrawal of the hormone, tetany and finally death result. When it is raised by excessive amounts of the hormone, marked depression, coma, and even death may result. In addition to affecting the blood calcium concentration, parathormone probably also acts indirectly in the transport of calcium from the alimentary canal to its place of deposit in the bony tissues. A moderate excess removes calcium from the bones, but if the injections are continued over a long period the calcium is replaced in the wrong position, in the metaphyses of the long bones. Some calcium salts may also be deposited in the soft tissues.

The relationship between vitamin D and the parathyroids is still obscure. There are indications that these glands are involved in rickets, and the vitamin protects to some extent against the effects of parathormone insufficiency, probably by improving calcium metabolism.

THE PITUITARY

This organ, known also as the hypophysis cerebri, occurs throughout the vertebrate series. In the higher animals it occupies the hypophyseal fossa of the sphenoid bone. While structural differences occur in the different species, it is possible in all higher animals to recognize two lobes, anterior and posterior. The posterior lobe is divisible into a nervous part (pars nervosa) and an intermediate part (pars intermedia). The pars nervosa is attached to the floor of the third ventricle by means of a stalk or infundibulum. In the cat there is a cavity in the pars nervosa, which communicates, through the infundibulum, with the third ventricle. In most animals, however, the cavity becomes small or disappears after fetal life. A pars tuberalis is described as extending forward from the junction of the anterior lobe and the intermediate part to surround the stalk and spread out over the base of the brain. This portion is of insignificant size in some species.

The anterior lobe is composed of columns of epithelial cells separated by vascular sinuses and some connective tissue. At least three kinds of cells are recognized: chromophobes, acidophiles (concerned with growth), and basophiles (concerned with reproduction). The chromophobes are usually the most numerous. From them the other cells appear to be differentiated. The basophiles are the least numerous. The pars intermedia is a narrow band of epithelial cells (chromophobes and basophiles) situated between the anterior lobe and the pars nervosa. It forms a sort of cap for the latter. The pars nervosa is composed of modified nervous tissue and contains no epithelial cells except some invading basophiles, very variable in number, derived from the pars intermedia. The pars tuberalis is an epithelial structure. The anterior lobe and the tuberal part have a rich blood supply; the nervous part has a much less abundant blood supply; and the intermediate part is almost entirely without blood supply in all mammals (Bailey), but as it is often only one cell thick this is not important.

The function of the pituitary is usually studied from the standpoint (1) of the anterior lobe and (2) of the posterior lobe including the pars intermedia. These parts have different origins, structures, and functions.

Anterior Lobe. The hormones of the anterior lobe are proteins, and the application of physical methods of separation and identification has greatly helped in the development of our knowledge concerning them. Six hormones have been recognized. These are the adrenotrophic hormone, prolactin, and the growth, thyrotrophic, luteinizing, and follicle-stimulating hormones, arranged here in their approximate order of increasing solubility in water.

The *adrenotrophic hormone* is essential for the complete functioning of the adrenal cortex. Removal of the pituitary gland causes this organ to degenerate and become a mere shell. The adrenal cortex may be maintained in the hypophysectomized animal by the injection of the adrenotrophic hormone.

The *growth hormone*, when it is injected into young rats or dogs, causes them to grow unusually large. This growth is not confined to the skeletal system only, as injected rats become very fat. Hypophysectomy of the young animal produces a dwarf which resumes its growth if the hormone is injected, though the other anterior pituitary hormones must also be given if full growth is to be realized. Clinical evidence, and also that from a race of dwarf mice, indicates that the acidophile cells of the anterior pituitary produce the growth hormone, as they are present in smaller numbers than usual in cases of dwarfism.

The *thyrotrophic hormone* is essential for the efficient functioning of the thyroid gland. It is, therefore, an important regulator of metabolism, and probably the other hormones cannot exert their full effects if it is deficient. This may explain the relatively poor activity of pure growth hormone in the hypophysectomized animal.

The three hormones concerned with the reproductive processes are the *follicle-stimulating hormone,* which causes the growth of graafian follicles; the *luteinizing hormone,* which causes ovulation and the growth of the corpus luteum; and *prolactin,* which is necessary to the latter in the maintenance of its secretion. Prolactin is also important for the maintenance of lactation. In the male the follicle-stimulating hormone is necessary for spermatogenesis, and the luteinizer for the secretion of the testicular hormone. These three hormones are treated in more detail in the chapters on reproduction. They are produced by the basophilic cells.

Besides these hormones, which have been isolated in a pure state, there may be others. Some crude extracts of the anterior pituitary have a diabetogenic effect, others are ketogenic, and others have been made with growth-promoting effects upon the mammary gland. No substances have been prepared in a pure state which exactly duplicate these activities of the crude extracts, and many workers believe that these effects are due to certain actions of known hormones upon metabolism and to synergistic effects due to the presence of two or more hormones in the extracts.

In the view of the number of hormones produced by the anterior pituitary, it is not surprising that removal of the gland, or its disordered function, has profound effects upon the organism. Cessation of growth, which is easily observed, is due to the absence of the growth hormone; lowered metabolism is due to the absence of the thyrotrophic hormone; certain qualitative disturbances of metabolism result from the absence of the adrenotrophic hormone. Complete cessation of sexual functions and the atrophy of the reproductive tract are the results of nonsecretion of the three hormones which maintain the reproductive system. These extirpation results may be deduced from the effects produced when the organs controlled by the anterior pituitary are, themselves, removed.

Excessive secretion of the growth hormone produces gigantism, and the results differ according to the time of overproduction. If this happens before the epiphyses of the long bones have closed, a normally proportioned giant results; if it occurs later only the extremities, the hands, feet, nose, and lower jaw, may be affected. Later still, the tendency is to cause arching of the spine and the production of a humpbacked condition.

Analysis of clinical symptoms of pituitary malfunction is complicated since certain hormones may be secreted in excess and others in smaller amounts than usual, and, as was indicated above, the time relations are important. Hence diagnosis of the many bizarre conditions found is difficult and has become a highly specialized branch of endocrinology. Stockard has shown that the unusual forms found in certain breeds of dogs are the results of hereditary factors which express themselves through altered pituitary secretion.

As the hormones are proteins, they cannot produce their effects when they are fed since they are destroyed by the proteolytic enzymes of the digestive tract. It is also unlikely that they will be synthesized for many years. Active groups or chemical combinations within the molecules have not been found, and it is probable that the molecule as a whole, or a large part of it including peptide linkages, is necessary for physiological activity. It is difficult to reconcile oneself to the idea that an organ with but few cell-types can secrete at least six hormones with such far-reaching effects, and the question has been raised whether the methods used for isolation, mild as they are, break down one, or perhaps more, giant molecules which are combinations of hormones. This is, at present, a field for speculation. Enough has been said to indicate that the anterior pituitary is a gland with important regulatory functions, and by some workers it is regarded as the organ which co-ordinates the activity of many of the endocrine glands. But in spite of its great importance it is not essential for life. Removal of the gland is not fatal, but living is continued at a lower plane than it is when the gland remains intact.

Antihormones. It has been shown by Collip and his co-workers that animals when injected repeatedly with certain hormones become resistant to them to the extent that the hormones are no longer effective. The serum of the refractory animal will antagonize the action of the particular hormone when the hormone and serum are administered to other animals. Antigrowth, antithyrotrophic, and antigonadotrophic substances have been demonstrated. It is doubtful whether this relation has any importance in the normal animal.

Posterior Lobe. This consists of the pars intermedia and the pars nervosa. The latter contains no epithelial cells except some basophilic cells derived from the pars intermedia. It consists of neuroglial cells and nerve fibers. Some of these cells have become differentiated to form pituicytes, which are characterized by their numerous processes. It has been generally believed that the cells of the pars intermedia furnish the active substances of the posterior lobe, but recent work makes this view doubtful. It is probable that some intrinsic elements, possibly the pituicytes, give rise to the secretion. According to one group of workers the secretion escapes by way of the stalk of the pars nervosa into the third ventricle, where it mixes with the cerebrospinal fluid. This theory is not generally accepted. The simpler conception is that the secretion leaves its place of production by way of the blood stream as is done by internal secretions in general.

Injection of Extracts. Injection of extracts of the posterior lobe produces a number of profound physiological effects as follows:

1. A distinct rise in arterial blood pressure, as illustrated in Fig. 165. The effect is more prolonged than that of adrenaline. Repeated injections may cause little or no rise in blood pressure but may cause a fall. A constrictor effect on the smooth muscle of the arterioles is responsible for the rise.

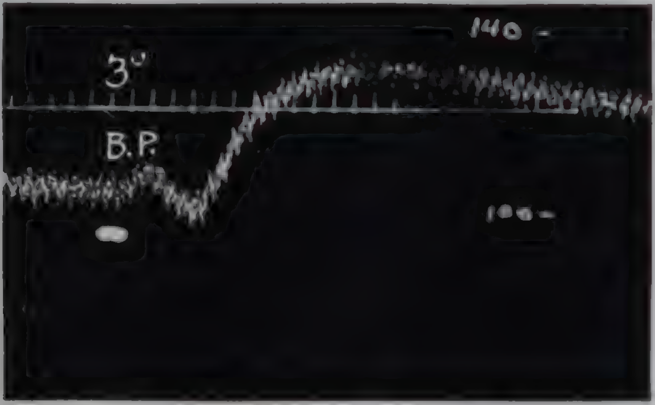


Fig. 165.—Effect of pituitary extract on blood pressure (pig). The injection (intravenous) was made at—. (Dukes and Schwarte, *Journal of the American Veterinary Medical Association,* 1931, 79.)

2. An antidiuretic effect (p. 409).

3. Stimulation of the muscular coat of the uterus, intestine, and bladder. These actions are believed to be on the muscle itself and not on the nerve supply. Both the pregnant and the nonpregnant uterus is stimulated by injections of postpituitary extracts. This is spoken of as the oxytocic action, which is very sensitive and is the basis of one of the methods of assay of pituitary preparations in which the nongravid uterus of the guinea pig is used. Pituitary extract may be employed to advantage in selected obstetrical cases.

4. Stimulation of milk flow. It has been shown in lactating animals of many species that injection of pituitary extract causes an increased flow of milk. Opinion is divided as to the mechanism of the action. Some hold that the mammary gland cells are stimulated directly, while others believe that the action is simply a hastening of the emptying of the gland because of stimulation of its smooth muscle.

Pituitary extracts have proved of little value therapeutically in stimulating a deficient milk flow.

Kamm and his co-workers have isolated two substances from the posterior lobe—one possessing the pressor effect (vasopressin, pitressin) and the other the oxytocic effect (oxytocin, pitocin). These results have been confirmed by others. Pitressin also gives the antidiuretic effect and stimulates the smooth muscle of the intestine. The effect upon the mammary ducts, about which more information is given in the section on lactation (p. 750), is due to oxytocin.

Removal of the Posterior Lobe. It is generally agreed that removal of the posterior lobe causes no evident disturbance of the animal's health, after the effect of the operation itself has disappeared. This does not necessarily mean that the posterior lobe is without significance in the normal animal, for its function may be taken over by some other organ, or the organism may in some other way compensate for its absence.

The Pars Intermedia. This part of the posterior lobe produces a hormone, intermedin, which causes expansion of the chromatophores of cold-blooded animals. The responses of frogs and chameleons to the color of their environment is determined by this action on the chromatophores so that intermedin may have a physiological function in these species. The hormone has also been demonstrated in the pituitaries of warm-blooded animals. Its significance in these animals is unknown, though there is some evidence that it is concerned in water metabolism.

THE ADRENALS

The two adrenals lie anterior to the kidneys, and they are usually larger in the female than in the male. Each consists of two parts, cortex and medulla. These parts, though united anatomically in most vertebrates, are distinct in origin and structure and also in function. Accessory adrenals are not of infrequent occurrence, especially in young animals. They are usually located between the kidneys and beneath the abdominal part of the aorta. They may consist of only cortical tissue or of only medullary tissue or of the two combined. Their possible presence must be kept in mind when considering the results of removal of the adrenals.

The cortex is much larger than the medulla. It consists of epithelial cells, which contain characteristic fatlike granules or droplets of various sizes. These droplets probably consist of cholesterol esters associated with lecithin. This lipid material is said to be small in amount in the adrenal cortex of herbivores.

The medulla consists of cells containing typical granules that stain brown with chromic acid or its salts. They are designated as chromophile granules. The chromophile cells of the medulla and those of the accessory adrenal tissue are sometimes grouped under the term chromophile system. The adrenals have an extremely rich blood supply.

Cortex. The cortex and medulla are two physiologically distinct organs. In most species removal of the adrenals is usually fatal in a few days, and it is certain that death is due to removal of the cortex and not the medulla (Stewart). Following are the symptoms of complete adrenalectomy.

For a day or two there is little evidence of any disturbance. Then the appetite fails, the rectal temperature falls, and muscular weakness appears. The basal metabolism is lowered, the glycogen stores are decreased, and the blood sugar level is reduced. Muscular weakness becomes severe, blood pressure is lowered, and death soon follows.

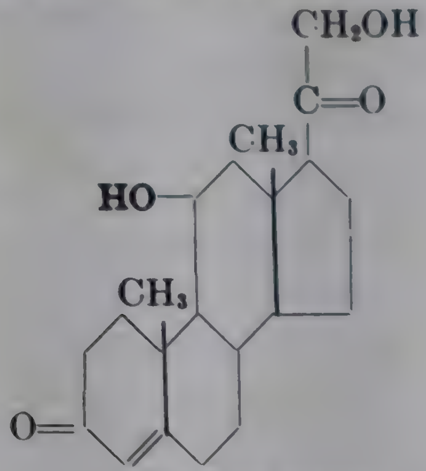
The rabbit is more resistant to complete adrenalectomy than are other animals. Twenty-five per cent or more of adult rabbits recover following the complete operation (Stewart).

A number of hormones have been isolated from the adrenal cortex, and it is not yet known how many are actually secreted by the gland. They are all steroid substances allied to cholesterol. Their physiological activities may be divided into three main classes: glycogenic activity, including the maintenance of muscular efficiency; cushioning the organism against shock due to toxins, trauma, or low temperatures; control of electrolytes and water metabolism. In the absence of substances controlling the last, sodium compounds are excreted by the kidneys and are not conserved in the body; the distribution of electrolytes and water in the blood and tissues is thus affected.

Control of each of these functions is not confined to any one substance but appears to depend upon the nature and position of side-chains about the basic molecular group. Thus, the glycogenic function is dependent upon the presence of an oxygen atom at the C 11 position; other arrangements are less well known. Glycogenic activity is possessed by corticosterone and 17-hydroxy-11-dehydrocorticosterone, while desoxycorticosterone and an amorphous fraction of unknown composition are important for renal function and the distribution of electrolytes. On p. 708 is the formula of corticosterone. The general structure is shared by the hormones of the adrenal cortex, testis, and ovary. An oxygen atom at the position indicated in heavy type (**HO-**) gives the power to affect carbohydrate metabolism.

Ascorbic acid, or vitamin C, is found in large quantities in the cortex. After cold shock the amount, together with that of cholesterol, decreases. It is therefore believed that the vitamin is concerned in the synthesis of cortical hormones, but the exact mechanism of protection against shock is not yet clear.

Addison's disease, characterized by a general lack of muscle tonus, feeble heart action, and abnormal pigmentation of the skin, results from degeneration of the adrenals. It can be controlled by the injection of a mixture of the cortical hormones. The disease does not occur as a clinical condition in animals.



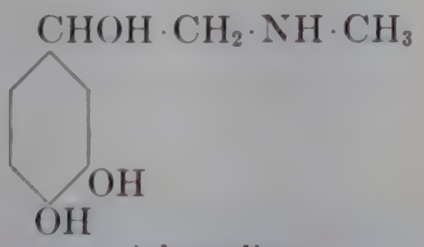
Corticosterone

That a cortical hormone in some way exerts a favorable effect on the nervous system is shown by experiments of Liddell and co-workers. They observed that a severe neurosis induced in sheep during motor conditioned-reflex studies could be alleviated by subcutaneous injections of an extract of adrenal cortex. It was also found that the vigor of the conditioned reflex in normal sheep was increased during the administration of an extract of adrenal cortex.

What appears to be an important endocrine *interrelation* is that of the cortex and the sex organs. It has been shown clinically that sexual precocity is not infrequently associated with tumors of the cortex, and that in the adult female the tumors produce masculinization. Androgenic (male) hormones have been isolated from the gland. That the adrenal cortex comes under the influence of a hormone produced by the anterior pituitary is indicated on p. 702, but it should be noted that while ablation of the pituitary does not cause death, removal of the adrenals does have this result. Part of the adrenal activity is, therefore, not under pituitary control. Recent work suggests that the part not controlled by the pituitary is that which secretes the electrolyte-control hormones.

The Medulla. The medulla is not necessary for life. It may be completely destroyed experimentally without in any way affecting the health or length of life of the animal when it has recovered from the effects of the operation itself (Stewart).

The Hormone of the Medulla. As stated above, the most characteristic thing about the medulla is the presence of chromophile granules in its cells. These inclusions are known to consist of the hormone of the medulla or to contain it as their chief component. Various names are given to the hormone: adrenaline, epinephrine, adrenin, suprarenin. It has been isolated, analyzed, and synthesized. Chemically adrenaline is dihydroxymethylaminoethylolbenzene. It is therefore closely related to the amino acid tyrosine, from which it is probably formed in the body. Its structural formula is:



Adrenaline

The Secretion of Adrenaline. Adrenaline is discharged into the blood leaving the adrenals. Its output is continuous, at least under experimental conditions. The secretion of adrenaline is controlled by secretory fibers in the splanchnic nerve, stimulation of which leads to a marked increase in the output of the hormone. Under these conditions the concentration of adrenaline in arterial blood becomes great enough to provoke distinct reactions, but under ordinary conditions the output is so small that it cannot be detected in arterial blood, the dilution probably being of the order of 1:1,000,000,000.

Injections of Adrenaline. Intravenous injections of adrenaline provoke profound physiological changes, most of which can be explained on the assumption that the hormone stimulates the sympathetic nerves of the affected organ. If the sympathetic nerve supply is excitatory, adrenaline will cause excitation; if it is inhibitory, adrenaline will cause inhibition. The exact place of action of the hormone is believed to be a substance that exists between the nerve endings and the tissues supplied, rather than the nerve endings themselves. The most striking effects of adrenaline injections may be summarized as follows:

1. Vasoconstriction and cardiac acceleration. The result of these actions is a great rise of blood pressure (Fig. 166). The vasoconstrictor effect is principally on the arterioles and capillaries of the splanchnic area and skin. Although the primary effect on the heart rate is acceleration, as the blood pressure rises the heart rate may be slowed because of reflex stimulation of the cardio-inhibitory center by the high blood pressure. Therefore when the vagi are intact, the blood pressure tends

to be self-limiting. On the contrary, when the vagi are cut or atropine is administered, the blood pressure may rise to a higher level.

2. Under certain conditions adrenaline may cause vasodilatation and a fall of blood pressure. This is especially likely to occur when the dose is very minute. Among the factors determining the nature of the action of adrenaline on the blood vessels are the organ studied, the body temperature, and the depth of anesthesia (Hoskins).

3. Dilatation of the bronchi.

4. Relaxation of the stomach and intestine and contraction of their sphincters.

5. Stimulation of certain glands. Thus there is a secretion of saliva, of tears, and in some animals (sheep, horse) a secretion of sweat.

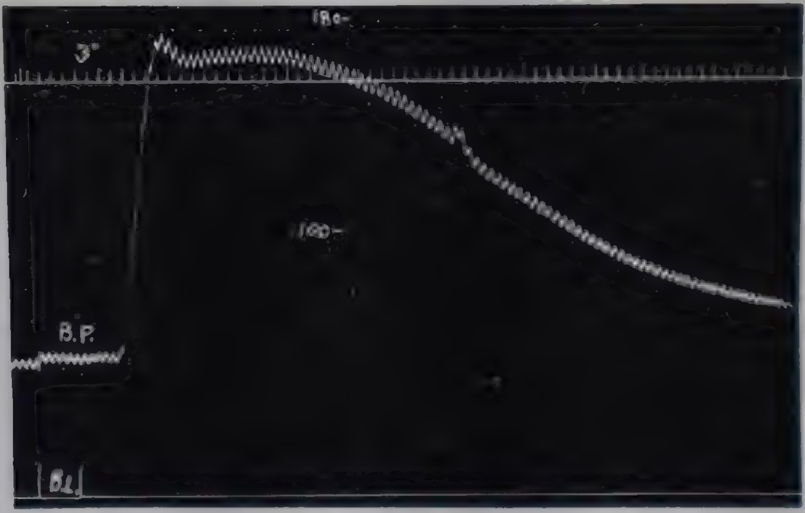


FIG. 166.—Effect of adrenaline on blood pressure of a 30-kg. pig. Spinal preparation. At the second signal 0.5 cc. of adrenaline chloride (1:1000) was given intravenously. The aortic depressor and carotid sinus reflexes were nonfunctional. The blood pressure could therefore rise sharply. (Dukes and Schwarte, *Journal of the American Veterinary Medical Association,* 1931, 79.)

6. Contraction of the pilomotor muscles. This causes erection of hairs and ruffling of feathers.

7. Dilatation of the pupil and bulging of the eyeball.

8. Variable effects on the uterus: contraction of the gravid and nongravid uterus in some animals; relaxation of the nongravid uterus in others.

9. Increased conversion of liver glycogen to blood sugar and muscle glycogen to lactic acid.

The Function of Adrenaline. The prevailing opinion at the present time is that the output of adrenaline under ordinary conditions is too small to be of any significance, if indeed there is any ordinary output at all. A view, however, which has much support (Cannon) relates to the action of adrenaline during emotional states, in emergencies, and the like. It is believed that under these conditions there is a sufficient increase in the output of adrenaline, because of reflex stimuli to the gland via the splanchnic nerve, to enhance definitely the action of the sympathetic nervous system at the points indicated above, the main effect being a shifting of the blood to the skeletal muscles to meet the emergency. Adrenaline is therefore sometimes termed the emergency hormone. Even this view, however, has not escaped criticism, and the physiological significance of adrenaline may still be regarded as a subject for research. (See also p. 657.)

In spite of inadequate knowledge regarding the normal function of adrenaline, the hormone has found a number of *therapeutic applications* because of its action on the circulation. The most important of these is "in combating acute circulatory collapse, especially in traumatic shock or accidents of anesthesia. Its effect, however, is of short duration and its use should be supplemented by measures that give more lasting benefit" (Rogoff).

THE PINEAL

This organ is present in most vertebrates. In the higher animals it is attached by a short stalk to the roof of the third ventricle. Various views are held regarding the histological structure and the physiological significance of the pineal. Following are some of the views as to its structure: (1) It is an endocrine organ. (2) It consists entirely of neuroglia. (3) It is a vestige. (4) It is similar to lymph nodes. The last two views are, according to Tilney, untenable. That the organ is endocrine in function is probable on histological grounds. This, however, would not exclude the possibility that it is made up largely of neuroglial tissue. Perhaps this tissue has taken on a secretory function. Certainly the character of the pineal cells would indicate a function different from that of neuroglia in general.

Although it is probable that the pineal is an endocrine organ, its function is unknown. Experiments made in an effort to determine its function have been of three main kinds: (1) feeding experiments, (2) injection experiments, and (3) extirpation experiments. Surgical removal in many species shows clearly that the organ is not essential to life. While in some instances the results of the different kinds of experiments have been negative, insignificant, or doubtful, the balance of evidence seems to indicate that the organ plays some part in the development of puberty and possibly in the early growth of the body. Tumors of the pineal are occasionally present in cases of sexual precocity.

THE THYMUS

The thymus is usually classified with the endocrine organs, although it is not certain that such a classification is justified. Assuming that it is an endocrine organ, it may be said to be the least understood of these. The thymus is a triangular organ, whose base rests on the pericardium. It consists usually of two lobes, loosely joined together. The upper portions extend into the neck on each side of the trachea. Morphologically the thymus resembles lymphoid tissue, and some workers believe that functionally it should be grouped with this tissue. That it is an important source of lymphocytes is generally recognized. A fact of considerable physiological interest is that the thymus attains its greatest development before puberty, a little after which time its involution sets in; but even in very old animals some thymus tissue persists.

Experiments made in an effort to determine the function of the thymus have, for the most part, yielded disappointing results. Extirpation studies in many species of animals show conclusively that the organ is not essential to life. Feeding thymus substance and, in the hands of most investigators, injecting thymus extracts have given doubtful or negative evidence.

Interrelations are believed to exist between the thymus and several of the other endocrine organs. The best known of these is with the sex glands. It has been shown by many workers that castration or spaying results in delayed involution of the thymus; however, it appears equally certain that thymectomy has no effect on the activity of the sexual organs (Andersen). Other interrelations have to do with the adrenals and the thyroid. Adrenalectomy in rabbits prevents involution of the thymus and causes regeneration in involuted thymuses, provided the thyroid gland is intact. Thyroidectomy in rabbits hastens involution and prevents the regeneration of the thymus that usually follows adrenalectomy.

SOME GENERAL CONSIDERATIONS

Considerable effort has been expended to explain differences in race, form, and temperament in terms of endocrine differences. Thus tall races are said to be hyperpituitary, and short races hypopituitary; dark races to be hypoadrenal, hairy races, hyperadrenal; excitable people or animals, hyperthyroid, beef cattle, hypothyroid; and so on. There is justification for some of the conclusions but others are most speculative. There is no doubt that the endocrines profoundly affect the metabolic processes and hence that they are involved in growth, differentiation, metabolic rate, and mental processes. But there are many endocrine glands and they are interrelated in such a complex way that it is difficult to explain any species or individual differences in terms of our present knowledge. Indeed, it is due to these interrelationships that much of the work on the endocrines is contradictory and puzzling. Removal or augmentation of one gland immediately affects the activity of all the others, so that we cannot obtain a clear view of the activity of the gland under investigation. Levels of endocrine activity vary with the environment and, in some degree also, with the heredity of the animal. The relationship between the hormones and the tissues upon which they react is usually quantitative but it, too, varies. Age and heredity are known to affect the results. Thus, the pituitary gonadotrophe is far less effective in the infantile subject than it is in the adult. Some strains of rats are more susceptible to adrenal deficiencies than others; strains of pigeons have been developed which differ in the response of their crop glands to prolactin by as much as twenty times; giant breeds of dogs seem to differ more in the degree of response to pituitary growth hormone than in their pituitary activity (Stockard).

In the general endocrine picture, it is evident that the anterior pituitary, though not essential to life, has a pre-eminent position, as it produces hormones that regulate the level of activity of the other endocrine glands. There is some evidence that it may share this pre-eminence with the adrenal cortex, but the relationships of the anterior pituitary are so marked that it has been described as "the conductor of the endocrine orchestra."

One point may be emphasized here. The hormones are chemical substances and are used up as they produce their effects. Consequently in replacement therapy injections have to be repeatedly given to maintain the proper level in the body. This is well illustrated in the case of insulin, which is familiar to everyone. Furthermore, the hormones are physiologically the most active substances known. The amount of thyroxine in the blood in man is certainly below one-hundreth of a milligram per 100 cc., and some other hormones, notably those of the sex glands, are even more active.

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Chapter XXXIX

THE FEMALE GENERATIVE ORGANS

NO PHASE of physiology holds a greater interest than the study of the phenomenon of reproduction. Our knowledge of its processes has been gained in very recent years as the reproductive tract was the last of the major systems to undergo detailed study by the physiologist. As our knowledge has broadened, it has become clear that nowhere else do we have so complex a series of actions co-ordinated with one another both in time and intensity to bring about the desired results. This delicate mechanism requires the perfect co-operation of the rest of the body. Consequently we find that when adverse conditions affect the other systems the reproductive mechanism is thrown temporarily out of gear, and it does not function normally again until the remote condition has been readjusted to bring the physiological processes once more into harmony. Conversely, sexual maladjustments, especially if physiological in nature, reflect themselves in the general bodily condition, producing in particular disturbances in metabolism. An example of this is seen in the excessive deposition of fat which is found in some castrated males and in their general tractability.

THE SEXUAL CYCLE

The female reproductive system has in most species a well-marked functional rhythm called the estrous cycle. Although each species has its own peculiarities, yet in the final analysis there is an essential similarity in the processes taking place in all female mammals, the chief differences being in the relative emphasis of the parts of the cycle.

The principal organ of reproduction in the female is the ovary, since by the production of ripe ova or eggs it sets the pace for the remainder of the tract, which must be adjusted to receive the ova and to carry them through to birth. This being so, the ovary has a dual function, the production of ova and the secretion of hormones. The latter cause the necessary adjustments of the accessory reproductive organs, or tubular genitalia, to take place. The estrous cycle or rhythm is divided into several more or less well-marked phases.

Proestrum. The first phase of the cycle is proestrum or the period of building up. During this phase the graafian follicle within the ovary is growing, principally by the increased secretion of follicular fluid. This fluid, which surrounds the ovum, contains the hormone estradiol. This is absorbed into the blood, whereupon it passes to the oviduct, or fallopian tube, and there causes a growth of the cells lining the tube and an increase in the number of cilia which are shortly to transport the ova to the uterus. At the same time a marked increase in the vascularity of the uterine mucosa takes place in preparation for the intense wave of growth which is soon to occur. The epithelial wall of the vagina increases in thickness, and as the cells bounding the lumen of the vagina are withdrawn farther from their blood supply they become cornified in certain species. The vaginal adjustment is well fitted to prevent possible damage to the wall when coitus occurs. In the dog the uterine part of these changes is accompanied by bleeding, the cause of which is not understood.

Estrus. The next stage is that of estrus, or the period of desire. This period is particularly well marked in the domestic animals. The changes of proestrum are intensified, and during this time the female will receive the male. The graafian follicle is now "ripe," or very turgid, and the ovum is undergoing certain maturation changes which have an important bearing on the hereditary possibilities that the egg will carry. In most of the species whose reproductive physiology has been studied, a very small proportion of the whole, this period is brought to a close by the rupture of the follicle, or ovulation. Follicular rupture is spontaneous in all known species except the rabbit, cat, ferret, mink, ground squirrel, and short-tailed shrew. In these animals estrus may last for a long time and ovulation usually occurs only as a result of coitus which initiates a nervous reaction. This will be discussed later in connection with the function of the anterior pituitary. If coitus is prevented in these species, ovulation does not take place and the graafian follicles degenerate and are reabsorbed. The changes normal in other species follow only if coitus with consequent ovulation has taken place.

Metestrum. During this time the cavity of the graafian follicle from which the ovum has been expelled becomes reorganized. The theca interna or fibroepithelial coat of the follicle grows in, carrying with it blood vessels. The granulosa cells, which have not all been expelled with the ovum, hypertrophy and become laden with fine lipid droplets. This new structure is the corpus luteum, an endocrine gland with important functions. It prevents the maturation of further graafian follicles, thus preventing the occurrence of further estrous periods for a time. It is essential for the implantation of the fertilized egg and for its nourishment during the first half of pregnancy, and is intimately concerned in the development of the mammary gland.

During metestrum the vaginal wall loses most of its new growth. The epithelial cells are desquamated, a process which is assisted by a heavy invasion of leucocytes, so that the epithelium returns to the resting state characterized by a layer of columnar cells. The uterus also undergoes a change in some species. The epithelium of the mucous layer or endometrium is denuded with the possible rupture of some capillaries.

Diestrum. During this phase, which is usually the longest part of the cycle, the corpus luteum is fully grown and its effect on the uterine wall is very marked. The endometrium thickens and the glands within this structure hypertrophy, increasing in size and complexity. The muscles of the uterus also develop. These reactions are obviously intended to produce a copius supply of uterine "milk" for the nourishment of the embryo prior to its attachment to the uterine wall and to provide a rich vascular bed for the placenta. If pregnancy supervenes this stage is prolonged throughout gestation, the corpus luteum remaining intact for the whole or most of this period. In the absence of a fertilized egg the corpus luteum undergoes retrogressive changes, and the cells become vacuolated and laden with large lipid droplets. These changes are followed by a rapid resorption of the corpus luteum. In some species, such as the cow and the ewe during the breeding season, the regression of the corpus luteum is followed by the growth of a new wave of graafian follicles which causes the induction of a new proestrous period. At the end of the breeding season in the unmated ewe the ovary becomes relatively quiescent, and the accessory organs, deprived of hormones to a large extent, tend to atrophy. This condition lasts until an external stimulus, as yet imperfectly understood, causes the ovary to enter upon a new cycle of activity. In the bitch, even though the eggs are not fertilized, the corpus luteum, with the uterine changes induced by its hormone progesterone, persists for the length of time usual in pregnancy. In the rabbit, after ovulation has been induced by coitus, a similar condition exists for 16 days if pregnancy has not occurred. Pregnancy in this species lasts for 32 days. As these diestrous periods are terminated by activities which normally occur at the end of pregnancy, such as nest making and the secretion of milk, they are described as pseudopregnant periods.

The estrous cycle may be summarized as follows:

A. Proestrum. Growth of follicles, thickening of vaginal wall, and increased vascularity of the uterine mucosa.

B. Estrus. Maturation and rupture of graafian follicle. Period of desire.

C. Metestrum. Growth of corpus luteum, desquamation of vaginal epithelium, some destruction in uterus.

D. *Alternatives:*

  a. Diestrum. Corpus luteum mature, rapid growth and maintenance, followed by involution, of uterine mucosa and glands.
  b. Pseudopregnancy. As in diestrum, but usually lasting longer and ending with reactions usually observed at the end of pregnancy.
  c. Pregnancy. Prolongation and intensification of the diestrous reactions under the influence of the embryo.

E. *Alternatives:*

  a. Proestrum. As above.
  b. Anestrum. Quiescence of the ovary and hence of the entire reproductive tract, followed eventually by proestrum.

In the higher primates the period of estrus is not marked, coitus being permitted at any stage of the cycle. Ovulation occurs in man about the twelfth day from the beginning of menstruation, while menstruation itself is preceded by the involution of the corpus luteum. The menstrual bleeding appears to be due to a rapid degeneration of the endometrium, a result of the withdrawal of the growth stimulus which has been provided up to this time by the corpus luteum hormone. The proestrous period is probably represented by the interval between menstruation and ovulation when the endometrium is increasing in vascularity. In young subjects, especially in the macaque monkey, menstruation may occur without ovulation. In this case the endometrium is vascular but has not entered upon the luteal, or glandular, phase so that the bleeding occurs from an unprepared endometrium. This phenomenon is imperfectly understood and complicates our views of the nature of menstruation. Possibly menstruation without ovulation may represent an intensified metestrous degeneration not held in check by a developing corpus luteum.

The nature of the discharge from the genital passage during the estrous cycle has been studied in a number of species. The constituents of the flow (mucus, white and red blood corpuscles, epithelial cells, and cellular detritus) vary with the stage of the cycle. This will be taken up in the discussion of the individual species.

Wild mammals are for the most part monestrous, that is, they complete but one estrous cycle per year. Under domestication the state of nutrition is increased, and the animal is given protection from the elements to a much greater degree than in the wild state. This has led, in many instances, to more frequent heat periods. An animal having periodic heats through the year is said to be polyestrous, and the cycles are called diestrous cycles. Some animals, such as certain breeds of sheep, exhibit diestrous cycles throughout only a part of the year and are said to be seasonal or seasonally polyestrous, this season generally being known as the breeding season.

First Appearance of the Estrous Cycle—Puberty. The attainment of sexual maturity is a gradual process. As the ovary increases in size as a whole, and the graafian follicles in particular enlarge, more of the follicular hormone, estradiol, is produced. This causes the growth of the tubular genitalia and the mammary glands. It also causes the production of the secondary characters which we regard as feminine, such as the typical female distribution of fat. As is well known, the development of full sexual maturity is a gradual process so that the attainment of puberty, which may be defined as the time at which reproduction may occur for the first time, is not associated with full reproductive capacity. This comes later. In animals such as the sow in which several young may be born at a time, the first two or three litters are smaller than the later litters. At the first few heat periods the number of ripened follicles is below the number which ripen at the height of sexual life. The time of puberty varies with the state of nutrition and with climatic conditions. Puberty is reached much earlier in animals kept in a high state of nutrition. Mares usually reach puberty by the second year of life. Küpfer states that the donkey reaches maturity in one year, but horses and donkeys allowed to run on the veldt in South Africa may be two years old before it is reached. Well-cared-for dairy heifers reach puberty at about the seventh month; range cattle, up to fifteen months. Küpfer states that Swiss cattle in central Europe mature at eighteen months. The earliest recorded parturition in a cow is one day short of a year (mother, 364 days of age). Ewes and sows breed at about six months; the sow, however, may mature somewhat earlier than this. Dogs and cats often breed at six months to one year of age; but a greater variation is common in both species.

Pregnancy. The estrous cycle is normally interrupted by pregnancy. In lower mammals conception can take place only during estrus, as this is the only time the female will permit coitus; and, as will be seen later, the ovum is short-lived, so that diestrous or anestrous coitus would be futile. The number of pregnancies in one year will naturally vary with the species and the duration of pregnancy. In the mare and cow only one pregnancy takes place per year. In some breeds of sheep, in sows, in bitches, and in cats, two pregnancies a year are possible. Occasionally mares are found that become pregnant only every other year, and this may also be true of cows under range conditions.

The estrous cycle reappears in many of the domestic mammals shortly following parturition. In the mare estrus recurs from eight to eleven days following foaling. The time may, however, be somewhat longer. The cow may ovulate from six days to seven weeks after calving. The sow frequently ovulates three to six days after delivery.

The estrous cycle is absent during pregnancy, although some females manifest heat during this period. The pregnant domestic rabbit commonly permits coitus and sometimes manifests intense libido. Cows are occasionally seen that come in heat at regular or irregular intervals during a part, or even all, of pregnancy.

The Menopause or Climacteric. Senile changes known as the menopause regularly take place in the genital organs of women at an average age of forty-nine years. This condition is not well understood in the domestic animals, as they usually die before this stage of life is reached, or are disposed of by their owners. Marshall states: "Mares have been known to produce young beyond thirty years, sheep up to twenty, and cats to fourteen." The available evidence suggests that the cessation of breeding is a more gradual process in the domestic animals than in man.

THE OVARY

The ovary has a dual purpose, the production of the egg or ovum and an endocrine function. The production of the ovum and its associated phenomena will be discussed first, and the endocrine relations later, as they are not readily understood until one has a clear conception of the cyclic changes in the tubular genitalia.

In all mammals the ovary apparently develops with germinal epithelium completely surrounding it except at the hilum. It retains this entire envelope of germinal epithelium in all species studied except those of the family Equidae. Küpfer states that in the young adult mare and donkey germinal epithelium covers the ovary except at the hilum, and that ovulation takes place over any part of the surface, the same as in other domestic mammals, but as the animal grows older the poles of the ovary grow out and are covered only by peritoneum. The only part of the ovary then covered by germinal epithelium is the ovultation fossa. From this time on, ovulation takes place from the ovulation fossa.

The ovary is divided into an inner medullary and an outer cortical portion (the medulla is not well defined in the mare). The medulla contains blood vessels, nerves, ganglion cells, stroma, and embryonic vestiges. The cortex of the ovary is made up largely of ovarian follicles and stroma. Beneath the germinal epithelium, or, as in the mare, the covering peritoneum, is a heavy membrane, the tunica albuginea. This is extremely heavy in the mare, making rectal palpation difficult and expulsion of ovarian follicles, cysts, or corpora lutea by digital pressure practically impossible. Nerves are derived from the renal and aortic plexuses of the sympathetic nervous system. These efferent nerves are believed to be mainly vasomotor in function.

Ovogenesis. The production of ova starts early in the prenatal period and was formerly thought to cease shortly after birth. The ova formed at this time were thought to remain and be utilized throughout the sexual life of the individual. Allen, in 1923, attacked this theory, claiming that in the mouse new ova are formed from the germinal epithelium at each heat period; in other words, claiming that ovogenesis is a continuous process throughout sexual life, just as spermatogenesis is known to be in the male. Continuous ovogenesis in adult life is now definitely claimed for the mouse, rat, guinea pig, dog, cat, monkey, and man. Its demonstration in such a wide range of animals would tend to indicate its occurrence in all mammals. Ovogenesis has been said to take place during pregnancy as well as during the estrous cycle.

The Ovarian Follicle. Soon after an ovum forms, it is enclosed in a structure known as the ovarian (graafian) follicle. This follicle first consists of a single row of epithelial cells surrounding the ovum. The follicle grows by multiplication of the epithelial cells and by a special formation of the surrounding connective tissue stroma, known as the theca folliculi. The theca is divided into an outer zone of typical stroma cells (theca externa) and an inner zone of epithelioid cells (theca interna). After a certain stage of growth, the epithelial cells begin to separate, producing an antrum filled with a light brown or yellowish, alkaline, albuminous fluid, the liquor folliculi. In this stage of development the ovum remains in a small hillock of epithelial cells, which projects into the antrum folliculi and is known as the discus proligerus. The ovum and its surrounding epithelium together are known as the cumulus oöphorus. The epithelial cells around the circumference of the follicle form the membrana granulosa. As the ovarian follicle matures the cumulus oöphorus becomes nearly or completely separated from the membrana granulosa. Ovulation takes place by a rupture of the follicle at the ovarian surface. The follicle at this time is under considerable tension. The ovum is gradually washed out with the liquor folliculi and is soon ready to be fertilized by the male sex cell. In a few instances it fails to be liberated when rupture occurs, being held in foldings of the wall as the follicle collapses (Long and Evans). (This is one reason why uniparous females occasionally pass over a heat period without conceiving.) The diameter of the ovum is about 0.13 mm. There is a surprisingly small variation in the different species of mammals.

Cyclic Development of Ovarian Follicles. The cyclic development of ovarian follicles plays a very important part in the reproductive phenomena in the female. Small follicles develop and then become atretic and disappear throughout the later part of prenatal life. From birth to puberty this process continues, but the follicles progressively enlarge before regression sets in. A six- or eight-month-old heifer calf may have two dozen to six dozen follicles in the ovaries, the follicles ranging in size from two to fifteen or even twenty millimeters in diameter.

The process of development and regression of follicles is continued throughout sexual life, but it is now cyclic in character. After studying ovogenesis and follicular changes in several classes of mammals (rat, guinea pig, dog, cat, and man), Evans and Swezy have come to the conclusion that a definite follicular cycle is manifest in all mammals, which involves follicles of all sizes in the ovary. They conclude that the life of the egg cell is probably shorter than that of any other group of body cells with the possible exception of the formed elements of the blood, new ova being formed with each succeeding cycle, largely during metestrum and anestrum. All follicles of the previous cycle which do not mature and ovulate become atretic, a process which reaches its height at proestrum and estrus.

Follicular Development During Pregnancy. In the mare, cow, and probably all other species, large follicles appear in the early part of gestation, atresia overtaking them at various stages of development. These follicles gradually decrease in number and size until in late pregnancy the ovaries are small, firm, and contain no large follicles. With the possible exception of the mare, ovulation does not occur during pregnancy. Cole, Howell, and Hart claim that several ovulations occur regularly in the mare between the 40th and 150th day of pregnancy; however, they did not recover tubal ova to prove this beyond question. It may be that the corpora lutea reported at this time are luteinized follicles that have not ovulated, as Evans and Swezy report in the pregnant rat. It would seem that further work should be done before this can be accepted as normal for the mare.

The Corpus Luteum. The corpus luteum is a temporary endocrine gland that forms from the wall of the follicle immediately following ovulation in the manner already described. During its functional life it is a highly vascular structure. Following ovulation the follicles collapse and present a folded appearance. There may be more or less hemorrhage at this time. In some species considerable hemorrhage seems to be the rule, while in others the reverse is true. The appearance of hemorrhage has led to the term corpus hemorrhagicum. More or less extravasation of lymph takes place because of injury of the blood vessel walls. In the rat, ferret, and dog, a complete redistention takes place, which is later resorbed as the corpus luteum develops.

The corpus luteum usually remains fully developed throughout pregnancy in all domestic mammals except the Equidae. It shows cellular degenerative changes in the cow at five months of gestation, but no gross involution is noticed.[1] The mare differs markedly from other mammals in that the corpus luteum undergoes complete involution during late pregnancy. As previously stated, Cole and Hart report ovulation in the mare during pregnancy. They also state that those follicles which ovulate form corpora lutea, as high as eleven being found in the ovaries at one time. After the 150th day of gestation they atrophy and in the latter part of pregnancy are no longer visible.

The corpus luteum undergoes rapid involution following parturition. Some animals ovulate very shortly following parturition, and in some rodents the corpora lutea that develop remain throughout the period of lactation (the corpus luteum of lactation), thus preventing the estrous cycle while the mother is lactating.

THE OVIDUCTS AND THE UTERUS

The oviducts or fallopian tubes are folded tubes lying in the outer fold of peritoneum that extends from the ovary to the uterus, the mesosalpinx. Their free anterior extremities open into the peritoneal cavity, and their posterior extremities are continuous with the cornua or horns of the uterus. The peritoneal opening of the tube is continued by the fimbria, an expanded portion of the mucous membrane which lies in close relation to the ovary. The oviducts convey the ovum from the peritoneal cavity to the uterus. The uterus is divided into a body and two horns or cornua. The horns are relatively long and the body is very short in all the domestic mammals except the mare, in which the body is nearly the same in length as the horns. The horns are straight and long in the bitch and cat, extremely long and folded in the sow, and curved somewhat like a ram's horns in the cow, ewe, and goat. In these species the inner surface presents rows of cotyledons or caruncles, which develop to form the maternal placenta in pregnancy. It is in the uterus that the young become attached and develop until the time of birth.

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[1] In a few cases the corpus luteum does not remain during the last stages of pregnancy in the cow but undergoes marked degeneration and is very small at the time of parturition.

The cervix is considered as a part of the uterus, but it will be discussed separately because it is both morphologically and physiologically a distinct organ. The nerve supply of the uterus is derived from the sympathetic and the parasympathetic. The sympathetic fibers are predominantly motor, the parasympathetics predominantly inhibitory. The uterus may contract by reflex action through the lumbar cord; for example, nursing causes contraction of the puerperal uterus.

Changes in the Tubal Mucous Membrane. The epithelium of the uterine tubes is simple columnar, some of the cells bearing cilia, others not. Cilia are practically absent in the tubes of the cow. In the pig Snyder describes a high columnar epithelium with a smooth, regular surface at estrus. This epithelium changes to a much lower type during diestrum, the nonciliated cells projecting above the surface of the ciliated ones and frequently being actually extruded into the lumen. Snyder also reports a cyclic change in the human tubes in which the columnar cells become tall and regular at the midmenstrual (ovulation) period. Thus the tall, regular epithelium is associated with the time of passage of the egg through the tube. The tubal epithelium is low and irregular during gestation. In some species such as the rabbit a layer of albumin is deposited on the egg as it passes down the tube.

Activity of Uterine and Tubal Muscle. The musculature of the uterus and tubes shows spontaneous contraction waves, which vary with the stage of the estrous cycle. By examining whole excised organs of the sow under warm oxygenated Locke's solution, Wislocki and Guttmacher determined that contractions are predominantly peristaltic in nature but may at times be antiperistaltic. They found that tubal contractions originated largely from the ovarian end of the tube and passed toward the uterus, and that uterine contractions originated somewhere in the horn and passed toward the cervix. Neither of these movements was necessarily complete, that is, one movement usually did not pass over the entire organ. Several peristaltic movements might be passing over the organ at one time. By their naked-eye observations they could detect little or no activity in the uterine or tubal muscle during the last few days of the estrous cycle. The tubal muscle gradually developed activity at the time of estrus, while the uterine muscle remained quiet until ovulation, when it became suddenly active. This activity remained until the corpora lutea were fairly well formed, and then it gradually subsided. In the immature animal they found the ubal and uterine muscle continuously active. In case of conception, omplete quiescence of muscular activity was not observed. Keye used trips of uterine muscle of the sow and recorded the contractions on a kymograph. Seckinger used a similiar method of determining tubal contractions in the sow. He observed that during estrus and early metestrum there is a rapid contraction of the musculature of the uterine tubes, while during the interestrous period the contractions are relatively slow. Keye reports that the uterine muscular contractions are strong during estrus, becoming irregular following estrus and gradually passing into a state of very slight but more rapid contractions eight or ten days after estrus. Rectal palpation in the cow affords a method of studying normal uterine contractions in a general way. These confirm the studies reported for the sow in that uterine contractions are strongest during the time of heat. During estrus the uterus is erect and feels firm (turgid). At other times of the cycle the uterus of the cow feels quite flaccid, but after being handled for a few moments it gradually increases in tone and may develop the same turgid state found during estrus.[1] If conception takes place, the turgidity of the uterus found during estrus is retained through early pregnancy. Tracings of the activity of the uterine musculature of the cow at different stages of the cycle are illustrated in Fig. 167.

The Course of the Ovum Following Ovulation. Upon liberation from the ovary the ovum is shed into the funnel of the oviduct, which is believed to invest the ovary more closely at this time, an adjustment which is brought about by contraction of smooth muscle fibers. It has been shown that when one ovary is removed leaving the fimbria and tube entire, and the other tube is closed, a normal pregnancy may follow. The ovum may therefore be liberated from one ovary, cross the intervening space in the peritoneal cavity, and pass down the uterine tube of the other side. It is unknown by what means the egg may be occasionally transported across the peritoneal cavity as in these cases. A very plausible theory is that the cilia of the fimbria beat toward the ovarian end of the tube creating a movement of the thin layer of fluid between the peritoneal surfaces, thus drawing the ovum with the current. This is probably augmented by the peristaltic action of the smooth muscle of the fimbria and tube. In the dog and cat the ovary is almost inclosed within the bursa ovarica; upon ovulation the liberated liquor distends the bursa and causes its thin free border to press against the surface of the ovary. By this means there is little chance of the ova escaping. It is certain, however, that many ova in mammals do not reach the uterine tubes and are lost in the abdominal cavity. The passage of the ova through the tubes requires three to five days.

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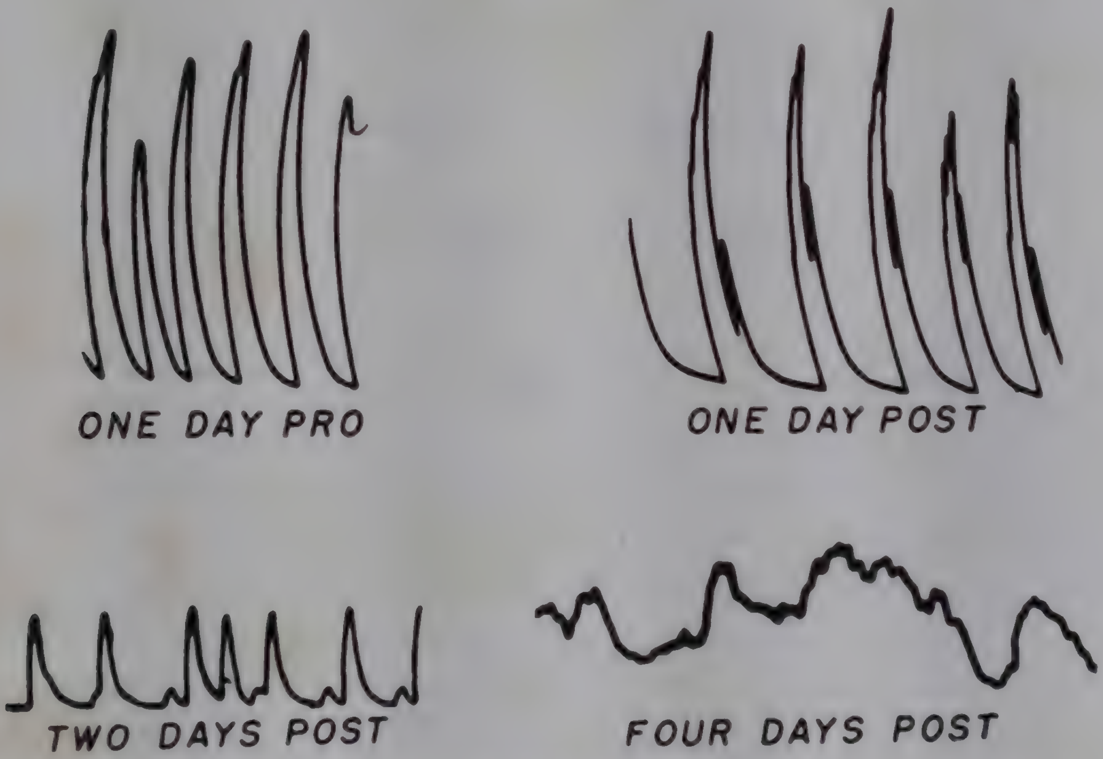
[1] The diseased uterus in the cow will not develop the same turgid state from handling that is found in the normal organ; this is of clinical importance in detecting metritis.

and the rate of travel is fast through the first and last thirds, taking but a few hours. Fertilization probably usually occurs in the funnel since the coating of albumin received during passage down the tube prevents the spermatozoa from entering the eggs. The fact that fertilization may take place before the ova even enter the tube is evidenced by the occasional occurrence of ovarian pregnancy.

Two theories have been advanced to account for the movement of the ova through the tubes: ciliary activity and peristaltic activity. Probably both mechanisms are involved but, since peristaltic movements are greatest in the oviduct during and just after heat, the latter appears to be the more important. The placement, or spacing, of the fertilized ova in the uterus of multiparous females must be the result of peristaltic activity as there are no cilia present on the uterine epithelium except in the gland crypts. In the cow the fetus usually lies in the horn of the uterus on the same side as the ovary from which the egg was liberated. Occasionally, however, the embryo is known to work through the body of the uterus and pass into the opposite horn. In multipara the number of fetuses in each horn tends to become equal regardless of the ovary from which the eggs were liberated. Warwick (1926) showed this to be the case by breeding semispayed sows. The



ONE DAY PRO

ONE DAY POST

TWO DAYS POST

FOUR DAYS POST

FIG. 167—Contractions of uterine muscle in relation to the estrous cycle in the cow. (From Asdell, *Patterns of Mammalian Reproduction*, Comstock Publishing Company, Inc.)

same number of fetuses was present in both uterine horns in spite of the fact that all the ova were from one ovary.

If the ovum is not fertilized in its passage through the uterine tube, it passes into the uterus and soon degenerates. Corner (1921) found ova of the sow in the uterus in an advanced state of degeneration by the seventh and eighth days after ovulation.

Maturation. During the formation of the male and female sex cells a process of division known as maturation or reduction division occurs. The primary object of maturation seems to be to halve the chromosomes in the sex cells so that their union will again equal the characteristic number for that species. This reduction division occurs during the formation of the secondary spermatocyte and oöcyte. The chromosomes are of both maternal and paternal origin and carry genes by which hereditary traits are transmitted. The process of maturation is illustrated in Fig. 168. In the case of the sperm, all four cells resulting from maturation are functional; but in the case of the egg one cell retains most of the cytoplasm, the other two constituting abortive ova or polar bodies. The first polar body is formed before ovulation in most species and afterward in a few (dog). The second polar spindle is formed, but the second polar body is not extruded unless the ovum is fertilized.

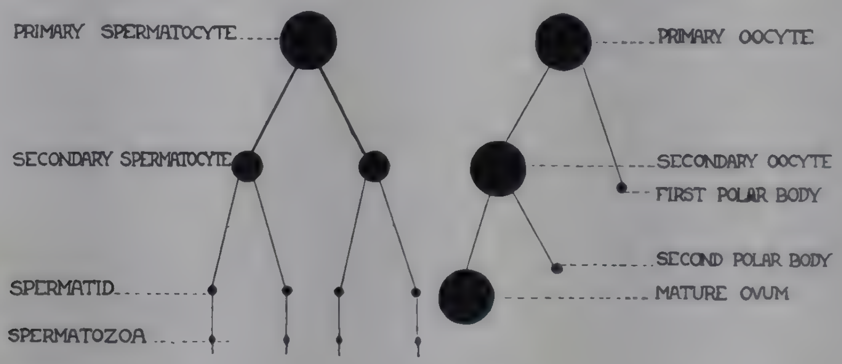


FIG. 168.—Schematic illustration of maturation of sperm and ovum. (After Boveri.)

Fertilization. It has already been stated that the ovum and sperm unite in the funnel of the oviduct. Just what specific force causes these cells to be attracted to each other is not definitely known. When the ovum is released it is surrounded by granulosa cells. These are dispersed by the first few spermatozoa to reach the egg. The sperms contain an enzyme, hyaluronidase, which dissolves the intercellular cement substance and causes the cells to fall apart. This permits the next spermatozoon an uninterrupted passage to the ovum.

In multiparous females, all the ova liberated at one heat period are seldom fertilized, or, at any rate, they fail to develop into normal young.

The number of young found in the uterus averages somewhat less than the number of corpora lutea in the ovaries. In the sow the number of ova lost has been found to be 20 to 30 per cent, and in some cases as much as 50 per cent, of the number liberated. Twin pregnancies in the mare are not nearly so common as double ovulations, as reported by Aitken, nor are twins and triplets so common in cattle as multiple ovulations are known to be.

Only one spermatozoon can normally enter an ovum. As the sperm cell enters its loses its tail-piece, and the egg becomes impervious to another sperm. This process is known as fertilization or fecundation. It should be remembered that the sperm consists essentially of a nucleus or head, a middle-piece or body, thought by some to carry the centrosome, and a motile part of tail-piece. Thus the sperm contains but little food material, while the egg consists of the nucleus and considerable cytoplasm containing food material known as yolk. (The yolk is greatly increased in the egg of the fowl and other lower forms of animal life, thus providing the source of nutriment for the developing young.) After union of the sex cells, the head of the sperm takes on the form of a true nucleus and moves toward the nucleus of the ovum. Thus are formed two nuclei, the male and female pronuclei. These unite to form the segmentation nucleus, and division starts at once in the formation of a new life. Details of the segmentation process must be left to the embryologist. The two-cell stage of the cow's ovum is shown in Fig. 169, and the four-cell stage can be seen in the oviduct of the dog in Fig. 170. The segmenting egg usually reaches a many-cell stage by the time it passes into the horn of the uterus. The most complete study of the early embryo of the higher mammals is probably that of Heuser and Streeter on the pig. According to these authors the rate of cleavage of the egg during the first seven days may be roughly stated as one cell division per day.

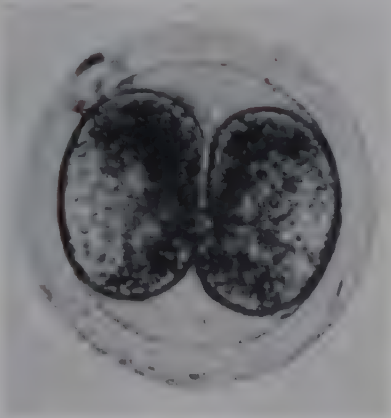


FIG. 169.—Photograph of the two-cell stage of a living cow's ovum. (From Hartman, Lewis, Miller, and Swett, *Anatomical Record*, published by the Wistar Institute.)

It is readily understood that neither the egg nor the sperm can form a new life in itself, since the egg requires the presence of the sperm before cleavage occurs. Many interesting experiments have been carried out in an effort to determine just what relation these two cells have to each other. In the sea urchin the spermatozoon has been placed with the yolk of a broken egg, and a larva developed, thus showing that the spermatozoon may develop if the necessary food is present. On the other hand, the egg has been subjected to certain environmental conditions—namely, placing in acid to form a membrane, then in hypertonic sea water for a time, and lastly returning to normal sea water—following which segmentation and development took place to form a normal larva. It seems that the spermatozoon contains the centrosome, which is absent in the egg, the centrosome being vital in the process of division.

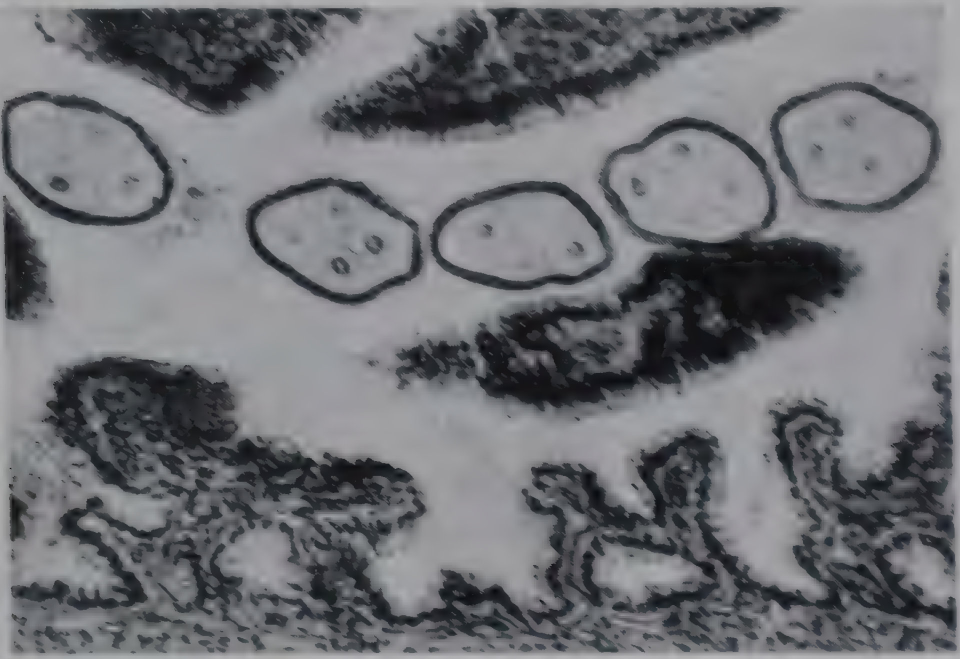


FIG. 170.—Photograph of the four-cell stage of segmenting dog's ova in the uterine tube. (Reproduced, by permission, from Evans and Cole, *The Oestrous Cycle in the Dog*. Memoirs of the University of California, 9, No. 2.)

The conditions to which the egg of the sea urchin was subjected apparently created a state in the egg very similar to that created by the spermatozoon, at least to the extent that cleavage was initiated.

The Placenta. The new organism during its intra-uterine life is dependent upon the mother for its nutritive material and for the removal of waste products. Thus it might be said to be parasitic upon the mother. There is an early differentation of cells into embryonic and extraembryonic groups; cells of the latter group constitute the trophoblast and develop into the primitive chorion, which carries nutritive material to the embryo until the development of the fetal membranes can be accomplished. The amnion now develops and surrounds the embryo, creating the amniotic cavity, which becomes filled with the amniotic fluid. The allantois develops from the hind gut and produces a cavity that is connected with the urinary bladder by a tube known as the urachus. The allantois carries with it blood vessels, which vascularize the chorion in all animals except primates. These outer layers of the fetal membranes are in intimate relation with the endometrium and are then known as the fetal placenta. While these structures are being built up by the developing organism, certain preparatory changes have to take place on the part of the maternal organs before nutritive exchanges can be established. It has already been stated that during estrus there is marked congestion and edema of the endometrium as well as vacuolar degeneration of the surface epithelium. Following the estrous period there is a marked thickening of the endometrium and development of the uterine glands. In pregnancy the edometrium is further modified to admit the attachment of the fetal placenta and it is then known as the maternal placenta. Two things are necessary before the endometrium will develop a maternal placenta: (1) a chemical (hormonal) sensitization of the endometrium, and (2) an irritant (probably mechanical) applied to the endometrium, which is supplied by the fertilized ovum. W. M. Allen has isolated from the corpus luteum the hormone causing the sensitization. It has been termed progesterone. Loeb scarified the endometrium of the guinea pig and found that during the period of development of the corpora lutea (luteal phase) there developed tumorlike growths resembling maternal placenta (deciduomata). If the corpora lutea were removed, deciduomata failed to develop. Since Loeb's classical experiments, similiar ones have been reported on other species of animals with practically the same results.

Classification of the Placenta. A placental classification of mammals is rather difficult to make, and seems to have no relation to the usual zoological classification. In the deciduate female the ovum seems to erode the endometrium in order to obtain attachment. In this type of placenta the entire endometrium is not involved; the placenta either constitutes a definite circular band or zone (zonary placenta) around the uterus as in the dog and cat, or else a disklike area (discoid placenta) as in the rabbit and monkey. At parturition the maternal and fetal parts of the placenta are so intimately united that a portion of the former is torn away with the latter. In indeciduate females the placenta affixes itself firmly to the surface of the endometrium but separates quite readily at the time of parturition. Indeciduate placentas are also of two types: the diffuse, in which the entire endometrium in involved, as found in the mare and the sow, and the cotyledonary (caruncular), in which the placenta develops only at definite elevated areas on the endometrium, as found in the cow, ewe, and goat.

The Nutrition of the Embryo. The mammalian egg contains but a relatively small amount of nutritive material. This is probably all used up in the early cleavages, so that this growing mass of cells soon has to look to the exterior for its nutriment. The ovum is thought to be nourished for a short time by contents of the uterine cavity commonly called uterine milk. This uterine fluid plays an important role in ungulates, more particularly in ruminants, but is probably less important in deciduate mammals. The fluid is derived from the secretion of the uterine glands and from a transudate of the surface epithelium, particularly lymph from the edematous mucous membrane. It contains leucocytes, red blood corpuscles and their derivatives, fat droplets, glycogen, inorganic salts, degenerative epithelial and connective tissue elements, and blood constituents found in the extruded lymph. Certain of these elements have been shown to be taken up by the trophoblast of the embryo. This is particularly true of the red blood corpuscles. Their hemoglobin is broken up into iron-containing and iron-free parts, the fetus making use of the former. In the pig trophoblastic cells arrange themselves around the crypts of the uterine glands and absorb the secretion of the glands, transmitting it to the fetal circulation. This same process is thought to take place in other species of ungulates, particularly sheep and cattle, but is discontinued in late pregnancy, whereas in the pig it continues over the greater portion of, if not throughout, pregnancy. The chorion is applied to the endometrium from the tenth to the fifteenth day in the pig, but the allantois does not begin to line the inner surface of the chorion until the third week. In the sheep mucosal attachment of the fetal placenta is said to be accomplished by the thirtieth day. Implantation in the mare is imperfectly known; permanent implantation probably occurs between the fortieth and seventieth days, although before this time a yolk-sac placenta exists. In the dog villi of the ectodermal layer of the embryo are said to become attached to the endometrium about the twentieth day, and in the cat about the twelfth day.

The fetus builds up a circulatory system of its own, which, in the placental region, is separated from the maternal circulation only by a very thin layer of tissue—in some species only by the endothelium of the capillaries and the epithelial lining of the villi. It is through these cells that respiration must take place as well as the interchange of other nutrient materials and wastes. To what extent the interchange is secretory or physical is not entirely known. The fetal blood differs but little in its composition from the maternal; hence diffusible materials may well be thought to be exchanged by the physical laws of diffusion, filtration, and osmosis. This may particularly be the case with sugar and salts from the mother to the fetus and with nitrogenous waste materials, as urea, uric acid, creatine, and creatinine, from the fetus to the mother.

The placenta is an effective barrier against the admission to the fetus of proteins or foreign bodies which might cause harm. It probably also protects the developing embryo against hormones circulating in the maternal blood stream which (as in the case of sex hormones) might influence its development.

Fetal Respiration. The blood in the umbilical arteries is venous in nature, carrying with it carbon dioxide and other products of metabolism. These are exchanged across the placenta for oxygen, sugar, and other substances needed for fetal growth, so that the umbilical vein returning to the fetus carries oxygenated blood. The embryo makes its own erythrocytes.

The Amniotic and Allantoic Fluids. The liquor amnii is found surrounding the fetus and within the amnion. It furnishes a water cushion around the fetus for protection, allows freer fetal movements, and prevents intra-abdominal pressures from molding the developing organism. At the time of parturition the amnion pushes into the cervix, thus serving as a dilating wedge. The amniotic fluid is slightly alkaline in reaction; it is mostly water but also contains protein, sugar, fat, and inorganic salts. The presence of urea and creatinine in the fluid suggests the excretion of urine from the fetus. Since the urachus connects the allantoic cavity with the urinary bladder, the allantoic fluid may be considered largely as excretory matter from the fetus. It contains sugar, mucin, inorganic salts, and certain other products that indicate urinary origin.

Pregnancy Changes in the Uterus. The uterus must undergo marked enlargement during pregnancy, and with this there must be a proportionate increase in the blood supply. The great increase in blood supply, particularly in the utero-ovarian and middle uterine arteries, is made use of clinically to diagnose pregnancy in the mare and the cow. The smooth muscle cells of the uterus show a marked increase in size (and possibly also in number as a result of connective tissue differentiation). Involution of the uterus following each succeeding pregnancy is not complete, that is, the organs do not come back to their former size. Thus the organs of animals which have passed through several pregnancies are much larger than those of virgins. In cotyledonary types, as the cow and ewe, when only one young develops, the cotyledons become much larger in the horn in which the fetus lies than in the opposite one. The maternal cotyledon in the ox is much heavier than the fetal cotyledon, but the reverse is true in the ewe. This is due to the fact that the cotyledon of the ewe is cup-shaped, the fetal placenta attaching on the inside of the cup, while in the cow there is no cup-shaped depression, the fetal placenta attaching over the outer convex surface of the cotyledon. The weight relationships between the fetus, uterus and membranes, and fluids during the gestation of lambs are given in Fig. 171.

Parturition. Many hypotheses have been advanced to explain the cause of parturition. All of them, however, seem inadequate and lack sufficient experimental support. Some factors are certainly at work that bring about the termination of the pregnant state with such extreme regularity, but their exact nature is still a mystery. The oxytocic action of the posterior lobe of the pituitary has been advanced as influencing parturition, but Smith, after destroying the posterior pituitary in the rat, claims normal pregnancy and parturition independent of its action. Oxytocin, of the postpituitary, has been shown to produce a more decided action on uterine muscle after the latter is sensitized with the hormone estradiol. Since estradiol is produced in constantly increasing quantities throughout pregnancy, the hypothesis has been advanced that the synergistic action of these two hormones is instrumental in parturition. Another probable factor is that while the corpus luteum is functioning uterine sensitivity to oxytocin is at a minimum. The corpus luteum degenerates at the time of parturition, and it is believed that the sensitiviy of the uterine musculature to oxytocin, which is thus restored, becomes a factor. It is difficult, however, to see how pregnancy is maintained in the mare if this is the decisive factor. A nerve center in the lumbar portion of the spinal cord was long thought to preside over normal parturition, but this region of the cord has been destroyed, and still parturition took place. Nerve stimulation at the time of parturition is reported to have but little effect upon the uterus. Another hypothesis which has been advanced is that the fetus, as a result of inadequate nutriment, produces a hormone which enters the maternal circulation and initiates parturition. Whether or not such a hormone exists, the failing nutriment may be a factor in parturition. Probably several factors culminate in bringing about parturition; it is possible to dispense with some of these without preventing the act. The fetus is expelled by powerful contractions of the uterine muscle assisted by contractions of the diaphragm and the abdominal muscles. After the mother is delivered of the young, the uterine muscle continues to contract, forcing out the fetal membranes (afterbirth) and checking hemorrhage from the maternal placenta. The muscular contractions constrict the uterus and produce a thickening of its walls, and in this

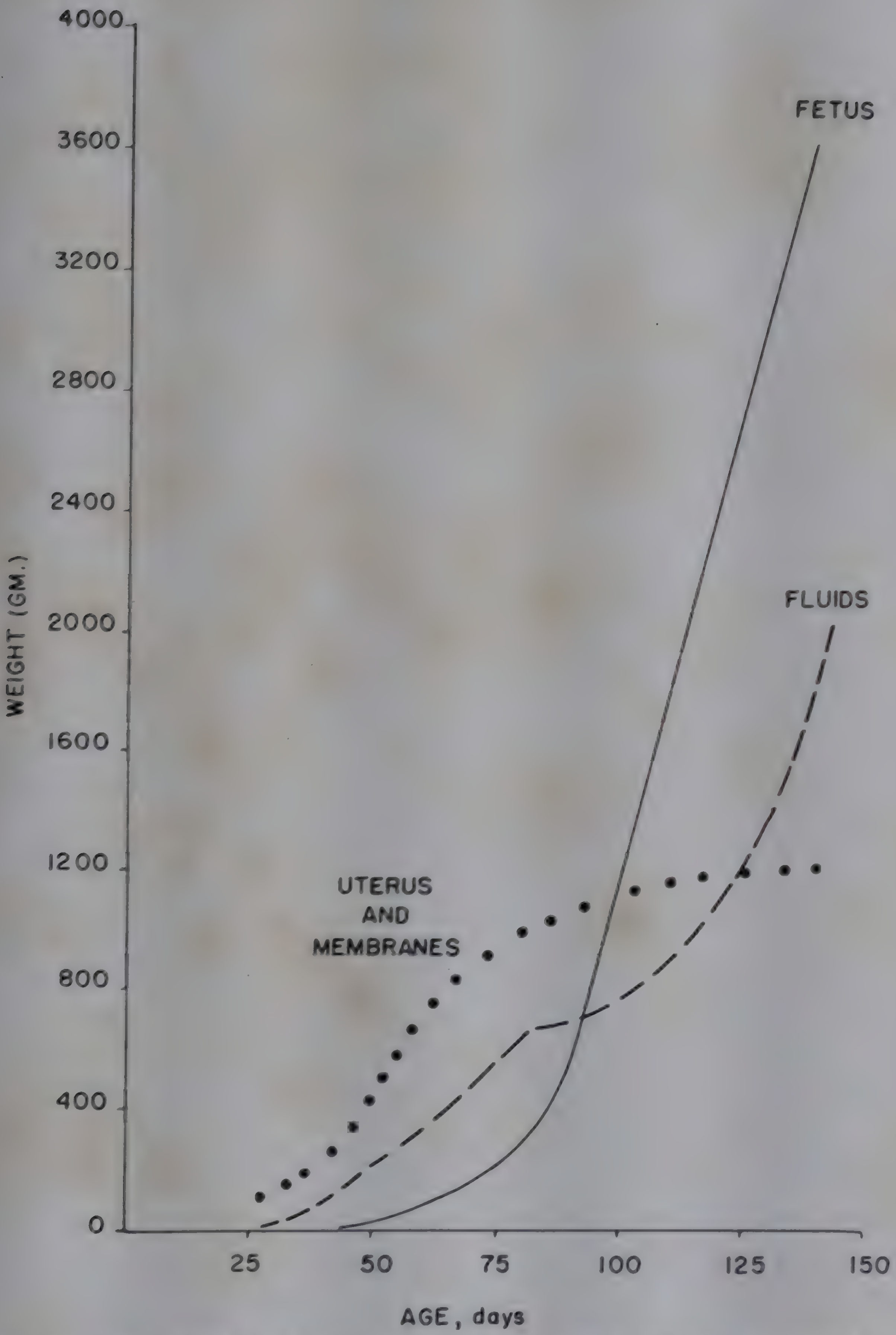


Fig. 171.—The growth of fetus, uterus and membranes, and fluids during the gestation of single lambs. (Data from Winters and Feuffel, *Minnesota Agricultural Experiment Station Technical Bull.* 118, 1936.)

way facilitate involution by expelling any material that may be left in the lumen of the organ. At the same time a resistance is placed against the large inflow of blood, which is now no longer needed. Expulsion from the vagina is largely caused by contractions of the muscles of the abdominal wall.

THE CERVIX

The cervix may be called the valve of the tubular genital tract of the female, for it is the most constricted portion and it produces a mucous seal that occludes the connection from the uterus to the exterior during pregnancy and diestrum. The powerful circular muscle of the cervix keeps the lumen of the organ closed at all times except during parturition, and it causes a marked folding of the mucous membrane. The cervix may be distinguished externally by its heavy wall, due to the great thickness of the sphincter muscle, and internally by its constricted lumen. In domestic mammals it is lined by a single layer of columnar mucous-secreting epithelial cells. The cervix of the cow is frequently spoken of as having branched tubular or alveolar glands. In reality this is not true, as each epithelial cell of the cervical epithelium constitutes a unicellular gland. The apparent complex glandular arrangement is merely a folding of the mucous membrane, which is erased by distention of the organ during parturition. This folding also causes the epithelium at times to appear stratified. The character of the mucus varies with different phases of the estrous cycle and with pregnancy. At estrus the mucus is greatest in amount, thin and watery allowing the passage of spermatozoa; it thickens during metestrum and becomes less in quantity and thick at diestrum. If pregnancy supervenes, the cervical mucus becomes very thick and rubberlike, efficiently sealing the canal. The glands, however, are not at rest after the seal is formed. Because of their activity the seal is probably replaced several times before parturition. This is particularly true in the cow, in which great strings of mucus are periodically dropped from the vulva throughout pregnancy. Some of this mucus, however, is secreted in the vagina. Interference with the cervical seal during pregnancy is likely to cause trouble. Aitken found in the mare that interference in any way was likely to result in abortion a few weeks later. The cow is not so sensitive in this respect as the mare. Cases are on record which show that the cervical seal may be broken and pregnancy continue. Mares have given birth to two living foals ten to twelve days apart, and cows have given birth to two living calves at a much greater interval. McNutt has observed a cow that aborted one fetus after five months of pregnancy, but carried another to term and delivered a vigorous, active calf.

The cervix of the mare is about three inches long and is never firmly closed in the nonpregnant state, but allows one or two fingers to pass into the canal. In the cow the cervix is about four inches long and very firmly closed. The canal is somewhat spiral, and if sectioned longitudinally it appears to be thrown into four or five deep folds which alternate with one another. If these primary folds are examined microscopically, they will be found to contain secondary and tertiary foldings of the mucous membrane.[1] At estrus the cervix is slightly relaxed, allowing an inner fold to protrude through the external os. This protruding fold is highly congested and appears reddish in contrast with the whitish character of the cervix and anterior part of the vagina. The cervix of the sow is relatively long and not entirely closed during the estrous cycle. The canal presents prominent transverse folds that continue for some distance into the vagina, making it difficult to distinguish the exact union of vagina and cervix. In the bitch the cervix is about a half-inch in length, not firmly closed, and projects into the vagina, forming a distinct point of demarcation between the two. The mucous membrane in the bitch is longitudinally folded.

THE VAGINA

The vagina is the portion of the tubular genital tract extending from the cervix to the urogenital sinus or vestibule. It is a highly elastic organ limited only in its expansion by the walls of the pelvic cavity, in which it lies. When examining the vagina in the mare or cow it frequently "balloons," or fills with air, expanding to the limits of space within the bony pelvis. The vagina serves as a birth canal at the time of parturition and admits the male organ in copulation. It is about eight to ten inches long in the mare and the cow; four to five inches in the ewe and sow; and three to six inches in the dog, depending upon the size and breed. The highly elastic character of the vagina makes it difficult to state the dimensions of the organ. The vagina is constricted at the junction with the urogenital sinus or vestibule. The cow is peculiar in that, in addition to this posterior sphincter, it also has a constriction or anterior sphincter just back of the external os. The anterior sphincter has a circular opening and is more marked in young animals, particularly virgin heifers. In the virgin it is frequently so pronounced as almost to defy the passage of a speculum to examine

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[1] This marked folding of the mucous membrane together with the copious mucous secretion that accompanies cervicitis makes this condition very difficult to treat by means of local application.

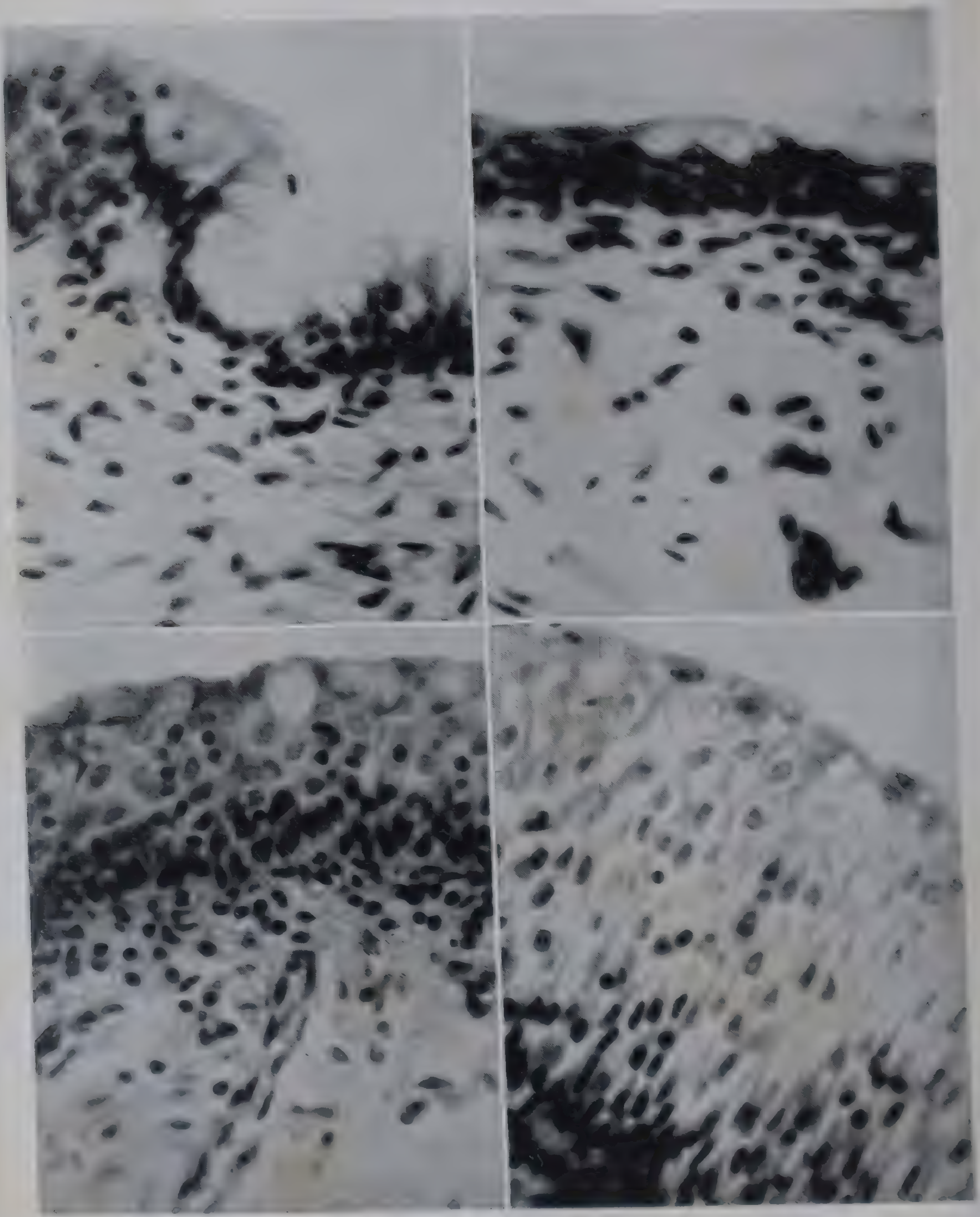


FIG. 172.—Changes in the vaginal epithelium of the cow. *Upper left*, section near cervix, two days postestrum. Note height of mucous cells. *Upper right*, section near cervix, twelve days postestrum. Mucous cells are collapsed. *Lower left*, section near vestibule, two days postestrum. Note squamous cells in outer layer. *Lower right*, section near vestibule, twelve days postestrum. The mucous cells are flattened and the epithelium is growing. (From Asdell, *Patterns of Mammalian Reproduction*, Comstock Publishing Company, 1946.)

the cervix. The vagina of the bitch narrows anteriorly; the large posterior part receives the bulbus glandis of the penis at coitus. Longitudinal folds extend the full length of the organ and are particularly marked in older animals.

The epithelial lining of the vagina is a true transitional type. It varies from a many-layered stratified squamous type at the time of heat (highly cornified in the rat, mouse, guinea pig, and dog) to a membrane consisting of only two or three layers of cells or, in some cases, even simple columnar cells in diestrum. This decrease in layers takes place by a desquamation of the surface cells. (See Figs. 172, 173, and 174.)

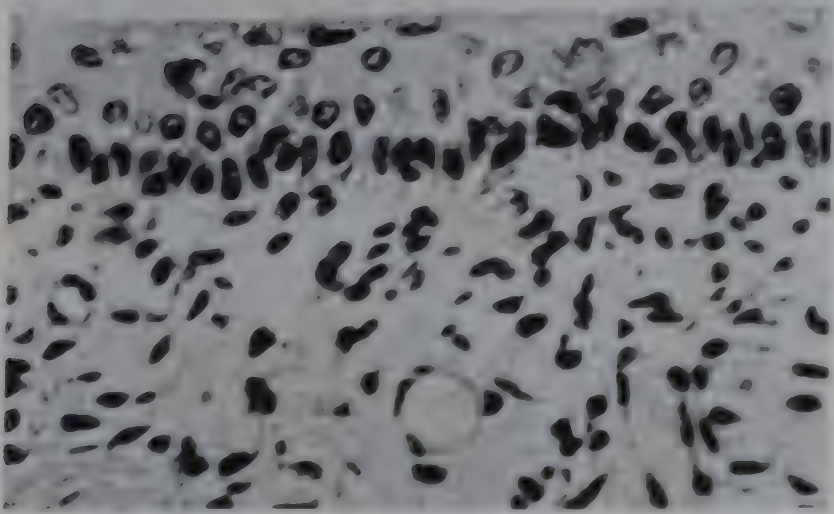


Fig. 173.—Photograph of the vaginal epithelium of the bitch at anestrum. The epithelium is low, tending toward a simple columnar type. (Reproduced, by permission, from Evans and Cole, *The Oestrous Cycle in the Dog*, Memoirs of the University of California, 9, No. 2.

THE HORMONAL RELATIONS OF THE REPRODUCTIVE SYSTEM

Several hormones concerned in reproduction have now been isolated, and, in some cases, synthesized. These developments have led to a much clearer understanding of the mechanisms involved but there are still gaps in our knowledge. It was indicated in the section on the anterior pituitary (p. 702) that three hormones are secreted by that gland which control the ovary and its production of hormones. The latter, in turn, control the reactions of the tubular genitalia, preparing them for the tasks which they perform.

The ovary secretes a number of hormones, the first of which to appear is *estradiol*. This is found in, and was first isolated from, the liquor folliculi of the graafian follicle. It is a steroid similar in basic structure to the hormones of the adrenal cortex. In addition, certain modifications of this hormone are also found in the body. Two of these, estrone and estriol, are probably secreted into the graafian follicle, and they are found in the urine when their concentration in the blood is high. Estradiol is not excreted as such but is first converted into estrone and estriol. All these hormones have similar physiological properties and are spoken of under the collective name *estrogen*. Injected into the body they produce the psychic symptoms of heat or sexual receptivity, cause the vaginal epithelium to grow and cornify, increase the capillary

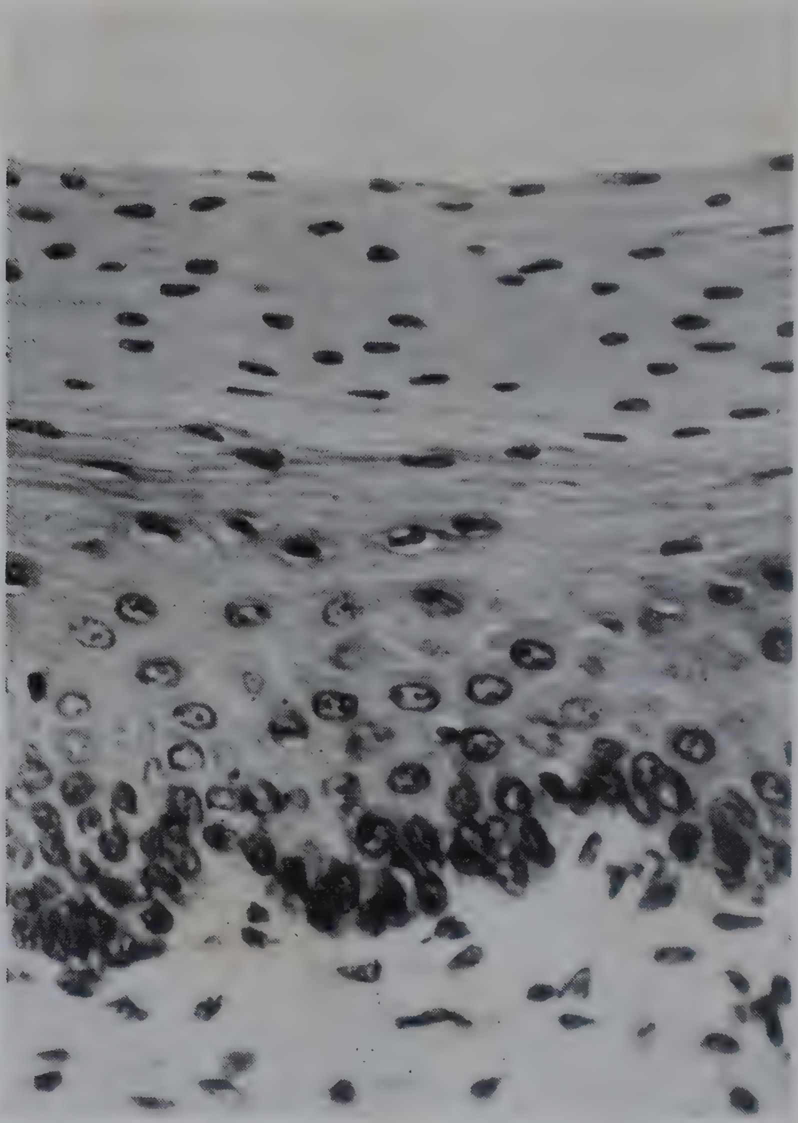
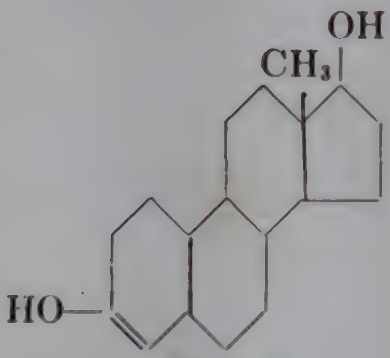


FIG. 174.—Photograph of the vaginal epithelium of the bitch at the beginning of proestrum to show the thickening and cornification of the surface layers. (Reproduced, by permission, from Evans and Cole, *The Oestrous Cycle in the Dog.* Memoirs of the University of California, 9, No. 2.)

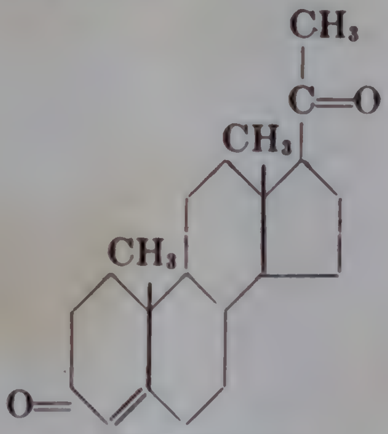
supply to the endometrium with resulting edema, cause the uterine muscle cells to grow and become sensitive to stimuli, and increase the sensitivity of the muscle of the oviduct. The reactions are obviously those of proestrum and estrus—periods in which the follicles grow and secrete these hormones. The site of their production is not yet settled; the granulosa cells have usually been regarded as the point of origin, but recent work indicates that the cells of the theca interna are involved.

Progesterone, also a steroid, secreted by the hypertrophied cells of the corpus luteum, inhibits the action of estrogens. It also causes development of the glands of the uterine mucous membrane and sensitizes the endometrium so that implantation and effective nutrition of the embryo are possible. These are the reactions observed in the normal female in diestrum, pseudopregnancy, and pregnancy. Removal of the corpus luteum in diestrum causes the return of heat within a few days, while its removal early in pregnancy almost invariably causes abortion. Both of these effects may be prevented by the injection of progesterone.

The formulas of estradiol and progesterone follow.



Estradiol



Progesterone

A third hormone, *relaxin,* is secreted by the corpus luteum but it has not yet been isolated in a pure state and its chemical structure is unknown. This hormone causes the relaxation of the pelvic ligament and partial decalcification of the pelvic bones so that the birth canal may be enlarged at the end of pregnancy to facilitate the passage of the uterine contents (Hisaw).

It is now possible to put these facts together to form an idea of the manner in which the female reproductive mechanism works. At birth, or soon afterwards, the ovaries contain many ova surrounded by granulosa cells. Gradually the anterior pituitary secretes the follicle-stimulating hormone (F.S.H.) in increasing quantities. This causes the multiplication of granulosa cells and enlargement of the follicle. Eventually some follicles become so large that enough estrogen is secreted to cause full growth of the tubular genitalia, development of the female secondary characters, and the onset of heat. The final growth of the follicles is so rapid that the proestrous and estrous changes in the vagina and uterus happen in a very few days. (In some species it has been found that psychic heat, or sexual receptivity, can be evoked more readily if a very minute amount of progesterone is injected with estrogen. This reaction may make it easier for heats subsequent to the first to occur, as corpora lutea may be present.) The estrogen secreted by the follicle now reacts upon the anterior pituitary causing a reduction in the secretion of F.S.H. and stimulating that of the luteinizing hormone (L.H.). These two hormones, acting together, cause the follicle to rupture, with the liberation of the ovum. The resulting cessation of estrogen secretion causes heat to cease so that ovulation is closely associated with the end of heat in most species. L.H. then stimulates the hypertrophy of the granulosa cells of the follicle and formation of the corpus luteum. The anterior pituitary now secretes prolactin, which stimulates progesterone formation by the corpus luteum, thus bringing the uterus into the condition necessary for implantation and the nutrition of the ovum. If this has not been fertilized, it degenerates and is not implanted, and the corpus luteum, after a length of life characteristic for the species, ceases to function. The anterior pituitary is then temporarily released from ovarian control and is able to renew the cycle by again secreting F.S.H.

If the female becomes pregnant, the placenta secretes large quantities of estrogens, which cause the anterior pituitary to secrete prolactin, under the influence of which the life of the corpus luteum is prolonged. Secretion of progesterone by this organ prevents the estrogens from bringing the female into heat and prevents the uterine muscle from becoming sensitive. Eventually the corpus luteum degenerates, owing to factors which are not yet understood but which are probably connected with placental failure. The uterine muscle then becomes sensitive, contractions follow, and birth takes place. These relationships are shown in Fig. 175.

There are some general interrelationships which emphasize the importance of the control exerted by the anterior pituitary. Thus, the horse has the highest content of F.S.H., then the pig, next the sheep, and the cow has least of all the domestic animals. The length of the heat period follows the same order, and the amount of estrogens required to induce heat in the ovariectomized female descends in the same order, except for the pig, for which data are lacking. Similarly estrogen excretion in the urine follows the same descending order. There is also some evidence that the length of life of the corpus luteum is related to the prolactin content of the anterior pituitary.

Seasonal Reproduction. The causes of seasonal reproduction are not fully known. Some species, for example, the horse and most fur animals, breed in the spring. In the nonbreeding season the anterior pituitary has a low hormone content. Injection of F.S.H. at this time stimulates the ovaries, and breeding may occur in the normal anestrous period. There is some factor which regulates the anterior pituitary. That this is external follows from the observation that when seasonal breeders are transferred from the northern to the southern hemisphere they soon adjust to the reversal of the seasons and breed in that season to which they are accustomed. Thus, horses breed about June in the United States; transferred to South Africa they breed in December. It has been suggested that an increasing gradient of light each day is the external factor involved. Thus it has been shown experimentally that exposure of spring-breeding fur animals, such as the fox, to an increasing daily amount of light in the fall and winter, normally the nonbreeding season, causes them to breed earlier than usual. In addition the F.S.H. content of the anterior pituitary increases. The increasing light gradient in some way activates this organ.

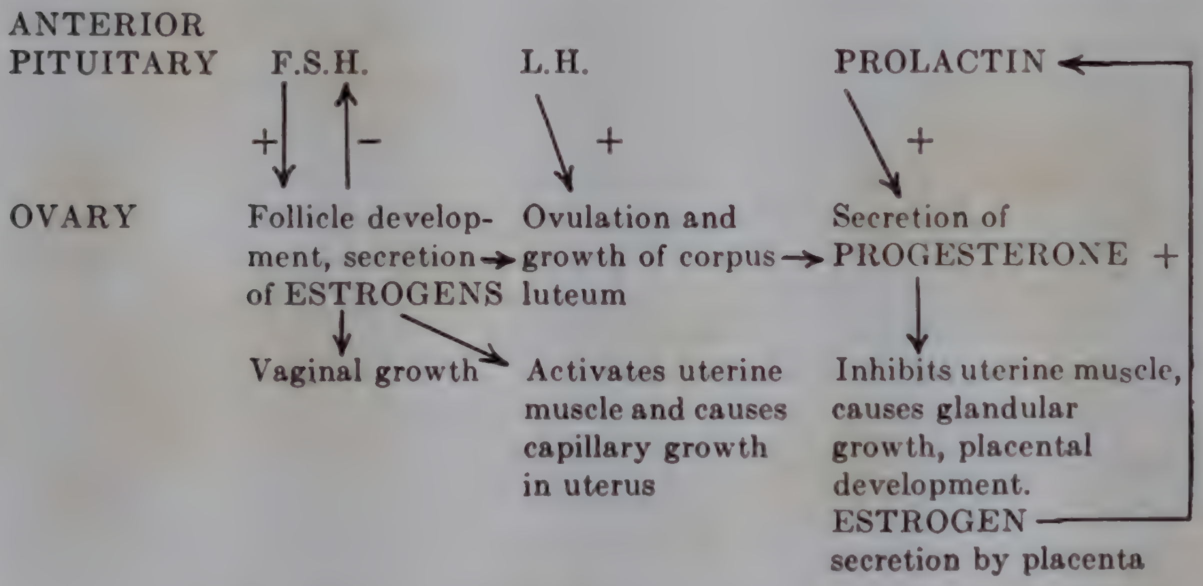

ANTERIOR PITUITARY
F.S.H.
L.H.
PROLACTIN
+
−
+
+
OVARY
Follicle development, secretion of ESTROGENS
Ovulation and growth of corpus luteum
Secretion of PROGESTERONE
+
Vaginal growth
Activates uterine muscle and causes capillary growth in uterus
Inhibits uterine muscle, causes glandular growth, placental development.
ESTROGEN secretion by placenta

Fig. 175.—Diagram illustrating hormonal control of estrous cycle and persistence of corpus luteum in pregnancy.

The reverse condition, found in sheep and goats, is that of the fall breeders. Again, breeding may be induced in the anestrous period by injecting F.S.H. By reducing the amount of light to which the females are exposed in the summer the onset of the breeding season has been hastened in some instances, but the results have not been as successful as the reverse treatment in spring breeders. Enough has been done, however, to show that the theory is correct and that the anterior pituitary is sensitive to changes in the amount of light in seasonal breeding females.

Pregnancy Gonadotrophins. In the human female a substance is found in the urine during pregnancy which has the properties of a mixture of F.S.H. and L.H. Its origin is in the placenta and it is known as chorionic gonadotrophin (prolan or P.U.). It has not been found in the urine of any other species, except for a short time during pregnancy in the chimpanzee and the rhesus monkey. Since it can be detected by observing its effects upon the ovaries of immature female rats and rabbits in heat, when urine containing it is injected, it forms the basis of a useful method of pregnancy diagnosis. In the mare from about 50 to 145 days of pregnancy a gonadotrophic hormone is found in the blood but not in the urine. This substance, also produced in the placenta and named equine gonadotrophin, is mainly follicle-stimulating in its action. It forms the basis of a good means of pregnancy diagnosis during the time in which it is secreted, and it is also collected and used as a gonad-stimulating preparation. It is also found in the blood of the pregnant ass. Although these hormones are found only in a few related species, they are not species-specific in their activity and they exhibit their characteristic reactions if they are injected into any species.

Pregnancy Diagnosis. The discovery of chorionic gonadotrophins, the biological significance of which is unknown, has led to their use in the diagnosis of pregnancy. This method can only be used in the mare and ass among domestic animals as these substances are absent from the blood of other species. Blood serum from a mare to be tested is injected into 21-day-old female rats and a positive diagnosis is read if the ovaries increase markedly in weight within 3 to 4 days. Another method is to inject the serum into rabbits in heat. If ovulation follows, the diagnosis is positive. The test can be made only between 50 and 145 days; at other times the gonadotrophin is not produced.

In other species, as well as in the mare later in the gestation period, the only available physiological test is the detection of large quantities of estrogens in the urine. These may be detected by injecting an etherial extract (after the ether has been evaporated off) of urine into spayed female rats. If the vaginal smear becomes cornified the diagnosis is positive. A color reaction, the Cuboni test, has also been developed which may be used instead of the rat test. This test depends upon the development of fluorescence in a benzene extract of the urine when it is treated with concentrated sulfuric acid. These reactions may be applied at any time after about 90 days in the mare and cow. In the pig they may be applied from the twentieth to the thirty-second day; after this they are not given until the seventy-fifth day, when estrogens again appear in the urine. The cause of this gap is unknown, but during the interval in which estrogens are absent from the urine they are also absent from the placenta.

Synthetic Estrogens. A large group of compounds with relatively simple formulas have been prepared which have the properties of natural estrogens, though they have not been found in nature. Of these, diethylstilbestrol and hexestrol are the best known. They differ from the natural estrogens in one respect: they are not destroyed when given by the mouth; hence they can be incorporated in the feed. They appear to have very limited use in the treatment of disorders of the reproductive system, but they may have some use in the induction of lactation.

Secondary Sex Characteristics. The gonads have long been known to be vital for the production of the secondary sex characteristics. This was first observed following the early castration of animals. In these cases it was observed that certain characteristics by which the sexes are readily distinguished failed to develop, and that there was also failure of the normal development of the remainder of the genital system. The castrates of both sexes develop toward a common type, which is called neutral. The form of the body, the growth of hair, and the distribution of fat are all noticeably influenced by the sex glands. All unsexed animals have the same type of skeleton: a narrow pelvis and a disproportionate lengthening of the limbs due to the fact that the union of the shaft and extremities of the long bones is deferred. In species where only the male possesses horns, castration results in their failure to develop, but this is not true where the horn is a characteristic of both sexes. In male mammals, massive bone and muscle development, thicker skin, more marked hair development, especially seen over the poll and frontal regions of the bull, and the crest of the bull and stallion, may all be classed as secondary sex characteristics. The voice of the male is also deeper because of a more marked growth of the larynx; the female larynx remains small, resembling more the neutral type. In the female, the thinner, smaller bones and the more refined features, together with the changes that take place in the pelvic bones, are some of the well-known secondary sex characteristics. If the ovaries are removed from the pullet, it will develop the bright plumage of the male but not the greater comb development. On the other hand, the capon also develops the plumage of the male but possesses a very small comb. Neither of these birds possesses the crowing instinct. From this it must be concluded that the brilliant plumage found in birds is a neutral characteristic, and that its suppression is a secondary female sex characteristic; on the other hand, large comb development and crowing are male characteristics. Early castration and successful transplantation of the glands of the opposite sex has resulted in the reversal of the secondary sex characteristics, the animals showing the characteristics carried in the grafted transplants. The characteristic female condition in poultry may be induced also by the injection of estrogenic hormones, and there is no doubt that estrogens are major factors in the development of secondary female characters.

THE MAMMARY GLAND AND MILK SECRETION

Morphologically the mammary gland is a cutaneous gland, but physiologically it functions in such perfect accord with the reproductive organs and is so vital to the normal development of offspring that it must be classed as an accessory gland of the reproductive system. It is one of the distinguishing characteristics of mammals and is developed for the purpose of nourishing the newborn. It is present in both sexes but develops normally only in the female. Mammae are distinguished according to their location as pectoral, abdominal, and inguinal. In the sow, bitch, and cat, two rows of glands extend from the posterior thoracic to the inguinal region; hence these animals possess all three groups of glands. The glands are usually paired. In the mare, cow, ewe, and goat, they are confined to the inguinal region. The cow usually has four quarters, two on either side, each of which is anatomically separate and drains through a separate lactiferous sinus and teat. In the sheep and mare there is usually one pair of glands. In all these animals the collecting ducts of the secretory tubules drain into the lactiferous sinus, which occupies the lower portion of the gland and the teat. The upper part of the sinus is subdivided by numerous connective tissue septa, which contain strips of smooth muscle. Milk escapes through the lactiferous ducts at the end of the teats. The ducts are guarded by a sphincter of smooth muscle. Nerves to the inguinal mammae are derived from the inguinal nerve, which is made up of ventral lumbar spinal branches (usually the 2nd and 3rd) and sympathetic fibers from the posterior mesenteric plexus. The blood supply of the inguinal mammae is derived from the external pudic arteries, which are accompanied by the inguinal nerves. Pectoral mammae are supplied by branches of the internal thoracic arteries.

Development of the Mammary Gland. The mammae show no marked development until the age of puberty. More development is shown before puberty in commercial milk-producing animals than in others. However, all development occurring before the first pregnancy is largely in connective tissue and fat rather than in actual gland tissue. With each estrus there is a slight "budding," or development of the gland duct tissue, which again recedes in the inter-estrous period. The development is quite marked in animals which show pseudopregnancy, such as the dog, in which it approaches the pregnant level and is accompanied by the secretion of milk. Ovarian influence is responsible for the mammary growth described above. A slight amount of a more or less serous secretion is frequently found in the newborn animal. This is associated with a transient development of the uterus and vagina and is evidently due to the passage of maternal hormones across the placenta. Small quantities of a watery fluid may be expressed from the udders of sexually mature virgin heifers. Turner reports no secretion from the udders of heifers spayed before puberty, but one heifer that was spayed before puberty and in which one ovary was successfully grafted into the neck muscles produced milk following estrous periods up to a maximum of 5.6 pounds daily. Considerable gland development was shown upon autopsy.

Hammond (1927) describes gland growth in first pregnancy in the cow as follows:

> Up to the 4th—5th month, growth of the granular connective tissue, vascular basis, and alveolar duct elements of the lobules is taking place. About the fifth month the character of the alveolar duct epithelium begins to change, and the parts of the alveoli which have completed their growth in length now begin to develop in thickness, or rather, diameter; the cavity produced is filled with a honey-like secretion containing a high percentage of globulin. Removal of this secretion apparently initiates true glandular activity and the formation of milk; when the honey-like secretion is not removed the secretory activity of the gland does not commence, but only further growth of the alveoli occurs.

Milk secretion can be definitely initiated several weeks before parturition in the heifer by removal of the secretion in the udder. In pluriparous cows marked udder development is not seen until shortly before parturition.

Hormonal Control of Lactation. Lactation has been shown to be largely under the influence of hormones. Vasomotor nerves undoubtedly play an indirect part in the secretion of milk, but secretory fibers are problematical. The inguinal nerves in cows, which carry the nerve fibers to the udder, have been divided without any noticeable change in milk yield. Mammary glands have been transplanted to other parts of the body and have undergone enlargement and milk secretion following a subsequent pregnancy. Such experiments show that mammary growth and lactation are under hormone control. The hormone estradiol brings about an initial budding and growth of the mammae in spayed animals and in males, but there is no milk secretion. Progesterone carries this duct development further, causing the alveolar or secretory portions of the gland to form. This hormone is ineffective unless it is preceded by the action of estradiol. A third hormone, prolactin or lactogen, from the anterior pituitary, is necessary for the actual secretion of milk. Secretion ceases if the pituitary is removed, and it has proved difficult to replace the normal function of the pituitary by an extract, probably because the influence is complex. As the mammary gland has an intense metabolism, it is very susceptible to metabolic upsets such as those produced by the effects of hypophysectomy upon the thyroid and the adrenal cortex. This may explain why crude extracts containing many pituitary factors are more effective than highly purified prolactin in replacement therapy.

According to Turner and his co-workers, the growth of secretory elements of the mammary glands is complete by midpregnancy, after which the only growth is by hypertrophy of the secretory cells. This seems doubtful, however, since in the lactating cow the second half of gestation is marked by a decline in secretion, which suggests that growth is occurring at this time instead of an increase of the secretory substances in the cells.

There is considerable controversy on the route of action of the ovarian hormones upon the mammary gland. By analogy with other physiological activities, one would expect that in a cycle of events, such as those involved in mammary development, the pituitary would act upon the ovary and that organ, in turn, upon the mammary gland. Early work by Asdell and Seidenstein supported this view. They removed the pituitaries from rabbits and injected estradiol and progesterone. Mammary development followed, as would be expected in the chain of events postulated. However, later work failed to confirm this direct action, and suggested that the ovarian hormones could work only when the pituitary was intact. In addition, it has been shown by Corner and others that crude alkaline anterior pituitary extracts can induce mammary development. However, the most recent work by Gardner and by others has produced further evidence that ovarian hormones are effective in the absence of the pituitary. The question naturally arises as to the completeness of the removal of the pituitary, particularly of the pars tuberalis. This structure sometimes extends well beyond the diaphragm of the sella turcica as a thin sheet over the base of the brain. It is doubtful, however, whether it is active since a remnant of the pars tuberalis does not produce the other hormonal effects of the anterior pituitary. Further evidence that the ovarian influence is direct is found in recent work by Folley and co-workers and by Speert. These workers painted ovarian hormones and also synthetic estrogens with similar properties on the undeveloped mammary gland. They were absorbed through the skin and induced growth only of the gland to which they were applied. If they were absorbed into the blood stream and induced the pituitary to secrete, development would be expected in all the mammary glands. The conclusion is justified, on present evidence, that the ovarian hormones induce mammary growth directly. However, as was mentioned above, pituitary extracts have been prepared which will cause the mammary glands to grow. Turner believes that there are two anterior pituitary hormones affecting mammary growth, one a *duct growth factor* and the other an *alveolar growth factor*. Their actions closely parallel those of estradiol and progesterone respectively. They differ from the other pituitary hormones as they are soluble in fat solvents, which indicates that they are not proteins; but Turner believes that they are not known estrogens as they are unstable to heat.

Mammary development, therefore, is caused by the two ovarian hormones, estradiol and progesterone, probably working directly, and possibly also by the two mammogens produced by the anterior pituitary, also working directly. Lactation requires an anterior pituitary hormone; prolactin, and the hormones of the adrenal cortex. The latter is indicated by the fact that lactation ceases with adrenalectomy and can be restored by the injection of a specific fraction prepared from the cortex (Brownell). In addition, hormones which affect metabolism, notably thyroxine and insulin, affect the level of secretion. The anterior pituitary hormone oxytocin produces an immediate flow of milk, either by causing a contraction of smooth muscle or by causing the cells to discharge milk that is already formed.

There is considerable evidence that the balance and even the nature of the hormones responsible for the various phases of mammary development differ between species. The guinea pig's mammary gland is very easily brought into a condition of secretion merely by the injection of estrogens, but that of the rat is most refractory. In the larger animals very little is known experimentally of the conditions under which mammary development may occur. Lactation often occurs spontaneously in the nonpregnant goat and is said to occur in two per cent of male goats, so that progesterone may play a minor part in this species also. But, according to Turner, lactation takes place in these instances from a duct epithelium and not from alveolar secretory elements. Asdell and co-workers have found that in those goats with a rapid decline in milk secretion injections of prolactin produce a marked increase in milk yield, while similar injections in high producers or at the peak of lactation have no such effect. This suggests that these extracts are ineffective where the pituitary produces enough hormone to allow the mammary gland to work at capacity. Azimov and Krouze, working in Russia with large numbers of cows, have found on the other hand that prolactin is without effect on the milk yield, while crude preparations cause a marked increase at any stage. This may be due to the presence of thyrotrophin in these crude extracts.

Hormonal Methods of Increasing Milk Flow. In the search for methods of increasing the milk flow a considerable amount of work has been done upon the effect of estrogens, both natural and synthetic, on lactation. Generally speaking, the natural estrogens, although they are necessary for building the gland, are harmful when they are injected during lactation. In quantities sufficient to produce an effect they appear to depress the pituitary so that the balance of hormones necessary for secretion is upset, with a consequent decline in lactation. If natural or synthetic estrogens are injected (the latter may also be fed), the gland is built up and a copious secretion results. In the cow the reproductive function is deranged as a result of the injections and nymphomania (continuous heat) or abortion follows. These consequences are not found in the goat. Sterile cows have been treated in this manner and have produced commercial quantities of milk, but not all cows respond.

Turner and his associates have experimented with the use of a synthetic thyroxine, or thyroprotein. This substance is cheap and easy to prepare, and it may be fed with the concentrate mixture. It acts by increasing the general metabolism, and the milk yield may be increased by about 20 per cent by its use. The fat percentage, which usually falls with an increase in milk yield, is also increased. Thyroprotein increases the heart rate and the respiration rate, and, as it has not yet been fed over long periods, it is not yet known whether cows can stand the sustained rise in metabolic rate. It is very effective over short periods.

The Letting Down of Milk. It is well known that some cows let down their milk more easily than others, and also that fright or rough treatment at milking time reduces the amount of milk that can be drawn off. Petersen has studied this problem in detail. Letting down the milk, that is, the expulsion of milk from the ducts into the lactiferous sinus, is controlled by smooth muscle cells in the walls of the ducts. Erection of the teats and ease of milking is controlled by a blood sinus at the base of the teat, which becomes engorged at milking time. If the cow is frightened she secretes adrenaline, which causes vasoconstriction, thus preventing the engorgement of the blood sinus and erection. Milking therefore becomes difficult. A contented cow, on the other hand, secretes oxytocin, which stimulates the duct musculature, thus letting down the milk. The secretion of oxytocin is caused by the conditioned stimuli that precede and the mechanical stimuli that accompany milking. As the oxytocic effect is transient, a greater quantity of milk can be obtained by rapid milking. Cows become conditioned to secrete oxytocin by stimuli which usually precede the milking process, such as the presence of the milker, the inevitable sounds, wiping the udder, etc. Therefore the whole milking process should be performed in a few minutes. Speedy milking also results in less pressure and wear and tear on the delicate tissues of the sinus, thus preventing injury which might admit infection.

Shortly after the beginning of milking there is an increase of intramammary pressure, which rises from an initial level of about 25 to 35 mm. Hg to 40 to 60 mm. Hg. This is caused by the above-described neurochemical reflex stimulation of the duct musculature.

The Secretion of Milk. Milk is produced by a true secretory process, as is shown by the fact that it has a different chemical composition from that of the blood from which it is derived. This is particularly true with regard to casein, lactose, and fats. The inorganic salts are identical qualitatively with those of the blood. Cow's milk is slightly acid in reaction (average *p*H 6.6). Simms reports the osmotic pressure of cow's blood plasma to be 260 millimols per liter, while that of milk is 282 millimols per liter. Making allowance for the calcium caseinate which is not in solution, the osmotic pressure of milk becomes about 260, the same as that of blood plasma, and is equal to 6.6 atmospheres at 37 degrees C. The freezing point is −0.55 degrees. Simms considers the mammary gland freely permeable to water. His experiments also tend to show that the distribution of inorganic cations between blood and milk is determined by the proteins. Certain substances may pass unaltered into the milk, and many drugs and certain dyes may be eliminated from the body through the milk. Some foods, such as turnips and rape, give a very unpleasant taste and odor to the milk of cows, particularly if fed shortly before milking.

Perfusion experiments have shown that lactose is produced in the gland by the conversion of blood glucose and lactic acid. About 35 per cent of the milk protein is derived from the blood amino acids. The origin of the rest is unknown. The origin of milk fat has led to much controversy. It was believed that it had its origin in blood phospholipids, but recent work has cast doubt on this view (Maynard and co-workers). The milk fats are now believed to be derived from fatty acids in the blood. The blood flow through the gland is most variable and is greatly modified by excitement, so that conclusions drawn from the analysis of samples of blood entering and leaving the udder must be treated with reserve. This accounts in part for the unsatisfactory state of our knowledge of the mode of action of the mammary cells.

No completely satisfactory explanation has yet been advanced for the facts that there is more fat in the last milk drawn and that quick milking yields more fat. Two theories have been advanced. The first and usual explanation is that the lighter fat rises to the top of the udder and is therefore drawn last. The other theory holds that fat is secreted separately from the rest of the milk and that it is more susceptible to changes of pressure within the gland. A complete and rapid release of pressure facilitates fat secretion and this takes place during the milking process. Fractional milkings of the human breast show similar, though less marked, changes in composition. This suggests that gravity is not the sole explanation.

Most of the milk given at a single milking is present in the udder of the cow at the time of milking (Gaines and Sanmann, Swett, Petersen). This is opposed to the older view that the capacity of the udder is not great enough to hold the milk given at a single milking, and that therefore most of the milk must be secreted during milking. About 40 per cent of the milk formed is stored between milkings in the spaces (milk cistern and ducts) of the udder, while the rest is accommodated by the stretching of the udder. Naturally, there is much variation in these figures with the yield of the cow and the interval between milkings. They may be taken as average figures for good cows just past the height of lactation under normal conditions. Pressure in the udder rises rapidly as it is stretched, but not before. This produces a back pressure which tends to shut off the blood supply by occlusion of the capillaries. It explains why more milk may be obtained by frequent milkings. Raising the udder pressure by injecting air, as in the old treatment for milk fever, reduces milk secretion for the same reason.

The Composition of Milk. For a detailed account of the chemistry of milk, the student is referred to books on milk (Rogers) or milk hygiene. Milk is a whitish or yellowish-white emulsion containing fat droplets in suspension. The proteins of milk are largely in a colloidal state and the other ingredients in true solution. The pigments of cow's milk-fat are largely the plant pigments carotene and xanthophyll, which are removed from the food. The greenish pigment of whey is riboflavin. The specific gravity of cow's milk ranges from 1.027 to 1.034.

The composition of milk varies greatly with species and breeds.

Variations are also found in individual animals. These are due to a variety of causes such as inheritance, food, phase of the lactation period, time between milkings, climate, sexual excitement, and season of year.

The average composition of milk is given in the accompanying table.

AVERAGE COMPOSITION OF MILK

	Water	Protein	Fat	Sugar	Ash	Total Solids
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Cow	87.+	3.4	3.8	4.9	0.72	12.+
Goat	86.88	3.7	4.+	4.6	0.85	13.+
Mare	90.58	2.+	1.14	5.87	0.36	9.4
Ewe	84.	5	4.+	4.+	0.9	16.
Sow	81	6.2	7.	4.75	1.1	19

It is seen that mare's milk is high in sugar but low in other solids. This seems to be peculiar to all Equidae.

During the first four days after parturition the milk, or colostrum, contains a high proportion of globulin which has been accumulating in the gland during the dry period. The proportion is much lower when the gland has been milked out right up to parturition. The globulin plays an important role in the nutrition of the newborn, for Howe has shown that the blood of the newborn does not contain globulin. In early life the wall of the intestine is permeable to globulin. Therefore when the calf is allowed to suckle, its serum globulin soon reaches the normal level, while if it is not allowed to suckle the normal level is reached very slowly, and the calf is usually weak and may not survive. This probably explains why, in the latter case, addition of egg white to the calf's diet is beneficial. The globulin fraction of the blood has associated with it immune bodies which are transferred to the calf, giving it some protection before sufficient time has elapsed for it to build up an active immunity.

The principal proteins in milk are casein, lactalbumin, and lactoglobulin, and the proportion among these varies greatly in the different species. Of these the phosphoprotein casein is found in much the greatest quantity. It is coagulated by the enzyme rennin.

Practically the only carbohydrate in milk is lactose or milk sugar. This is readily converted into lactic acid by bacterial action to produce sour milk. The fats of milk are largely olein, palmitin, and stearin. Small quantities of lecithin and cholesterol are also present. Calcium phosphate and potassium salts are plentiful in milk, and small quantities of magnesium and sodium chlorides and a trace of iron are found.

Traces of several other metallic elements are also reported. All vitamins necessary to the growth of the young are usually present in milk. It has been shown, however, that the amount of certain vitamins differs with the food supply; for example, cows fed upon dry foods during the winter months give a much smaller amount of vitamin A in the milk than those that receive succulent foods in addition to the dry ration.

Cellular constituents also normally occur in milk. These consist of epithelial cells, epithelial cell nuclei, and leucocytes in varying numbers. All forms of leucocytes can be seen in milk if it is stained with blood stains. Normal milk should probably not contain more than one-fourth million leucocytes to the cubic centimeter, although a count up to one million is usually considered normal.

Duration of Milk Flow. The duration of lactation in the various animals depends largely upon the needs of the offspring. In the cow the length of the lactation period is usually about 10 months. In many high-producing cows this period is somewhat longer, and, indeed, it is frequently difficult to obtain a rest period for the animal before another lactation period begins. Frequent milkings increase the total yield of milk during a lactation period and also increase the duration of the lactation period. It is well known that if the milk is not withdrawn from the mammae at frequent intervals, the glands gradually cease functioning. Spayed cows may lactate for long periods of time (several years). Milk secretion declines much more rapidly in pregnant cows after about the fifth month of pregnancy than in nonpregnant cows.

SPECIAL REPRODUCTIVE PHENOMENA IN THE DOMESTIC ANIMALS

The Mare. The breeding season of the mare is usually in the spring, from March to July, but if she is not bred at this time she may continue to experience estrous cycles for a variable period depending on the individual. The duration of estrus is variable; 2 to 11 days may be considered normal with an average of 6 days. The interval from the end of one heat to the beginning of the next is about 16 days but is extremely variable. Ovulation occurs from 1 to 2 days before the cessation of estrus. The time of service is important since the spermatozoa have a fertile life of 1 to 3 days; so, in the case of mares with a long estrous period, service should be repeated every 3 days to make sure that fertile sperms are present when ovulation occurs. Experience has shown that early service is associated with very low fertility and that the chances of impregnation increase as the service time approaches to ovulation time. Among range horses or mountain ponies, where the stallion repeatedly mounts the mare, fertility is over 90 per cent; while among hand-bred mares the average fertility is about 50 per cent, a figure which could be improved by paying more attention to the time relations (Hammond). The mare usually comes in heat again from 4 to 14 days after parturition and remains in heat until 11 to 20 days. This is known as the foal heat, and service at this time is said to be associated with greater fertility than at other times. The external signs of heat are general irritability, frequent urination, and movements of the clitoris. The filly comes in heat first at about a year old.

The ovary of the young filly, and also that of the young ass, is normal in form but, as growth proceeds, the poles grow inward until the whole ovary, except for a narrow groove, becomes invested with connective tissue. Ovulation occurs from this groove, or ovulation fossa. The follicles are remarkable because of their enormous size when compared to those of other domestic species. Seaborn and Aitken have contributed much to our knowledge of them. The follicle may reach a diameter of seven centimeters at the time of ovulation, and it contains from 50 to 80 cc. of fluid. Seaborn states that the weight of the ovaries varies from 25 to 172 gm., depending upon the stage of the cycle—a variation due to the large fluctuation in follicular size. During metestrum the ovaries are small, containing only small follicles. As a new cycle approaches, several follicles advance to two, three, or even seven centimeters in diameter. Those that rupture do so between four and seven centimeters. Ovulation takes place during the latter part of estrus; and as a rule only one follicle ruptures, but two not uncommonly do so. The remainder of the follicles recede rapidly after ovulation and soon disappear. The ovaries do not alternate at ovulation time; one may ovulate several times in succession. In case of double ovulation the follicles may both be from one ovary or one from each ovary. On rectal palpation the ovarian follicles of the mare feel tense and rather deep-seated but distinctly fluctuating.[5] The follicle softens before rupture and this is a better indication of pending ovulation than the size.

Considerable hemorrhage into the former antrum of the follicle is very common, although many corpora lutea develop in which it is absent. When any considerable amount of blood clot forms, it remains

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[5] It is evident from this description that many writings appearing in veterinary literature describing cystic ovaries in a mare are describing nothing more than normal, functional organs. To what extent cystic ovaries are present in the mare is not known. In an apparently normal mare which was embalmed for anatomy dissection, ovaries were found larger than a man's head. Cysts six or seven inches in diameter were found in both ovaries, yet this mare was several months pregnant. The fetus and membranes were normal (McNutt).

THE REPRODUCTIVE CYCLE IN DOMESTIC ANIMALS

Species	Nature of Cycles	Duration of Cycles (days)		Duration of Estrus		Time of Ovulation	Duration of Pregnancy (days)		Age of Puberty
		Average	Variation	Average	Variation		Average	Variation	
Mare	Polyestrous, seasonal in spring	22	16–30	6 days	2–11 days	1–2 days before end of estrus	336	329–346	One year
Ass	Polyestrous, seasonal in spring	—	21–28	—	2–7 days	Last third of estrus	365	—	One year
Cow	Polyestrous, all year	21	18–24	14 hours	8–30 hours	14 hours after end of estrus	282	274–291	4–8 months
Ewe	Polyestrous, seasonal in fall; more extensive in some breeds	16½	14–20	35 hours	1–3 days	At end of estrus	150	140–160	First fall
Goat	Polyestrous, seasonal in fall	About 21	15–24	2½ days	2–3 days	Toward end of estrus	151	140–160	First fall
Sow	Polyestrous, all year	21	18–24	2–3 days	1–5 days	Toward end of estrus	113	110–116	3–5 months
Dog	Monestrous, spring and fall	—	—	9 days	4–13 days	Near beginning of estrus	60	58– 63	Very variable

THE REPRODUCTIVE CYCLE IN DOMESTIC ANIMALS (*Continued*)

Species	Nature of Cycles	Duration of Cycles (days)		Duration of Estrus		Time of Ovulation	Duration of Pregnancy (days)		Age of Puberty
		Average	Variation	Average	Variation		Average	Variation	
Cat	Seasonally polyestrous, two or more seasons a year	—	15–21	4 days	?	Induced, 26–27 hours after coitus	64	?	Very variable
Mink	Polyestrous, February-March	—	—	2 days	?	Induced	50	41–60	One year
Fox	Monestrous, December-March	—	—	—	2–4 days	Near beginning of estrus	52	49–55	One year
Ferret	Monestrous, spring and summer	—	—	Several months	—	Induced, 2–3 days after coitus	42	Small	?
Rabbit	Polyestrous, all year except tendency toward anestrum in summer	—	—	A month	?	Induced, 10½ hours after coitus	31	30–32	About 6 months

as a deep brown or almost black, central, gelatinous mass around which the yellow-colored corpus luteum is built. The corpus luteum never reaches the size of the follicle from which it came and is either round or elongated (pear-shaped) with a narrow neck leading to the point of rupture. The life of the corpus luteum and other phases of the ovarian cycle in the mare are shown in Fig. 176.

The vaginal smear is not a good means of diagnosing the reproductive state. Cornified cells tend to increase in numbers as the mare comes in heat, but a better sign is the moist and glistening vaginal mucosa at this time. Service is followed by an invasion of leucocytes, which disappear if heat continues.

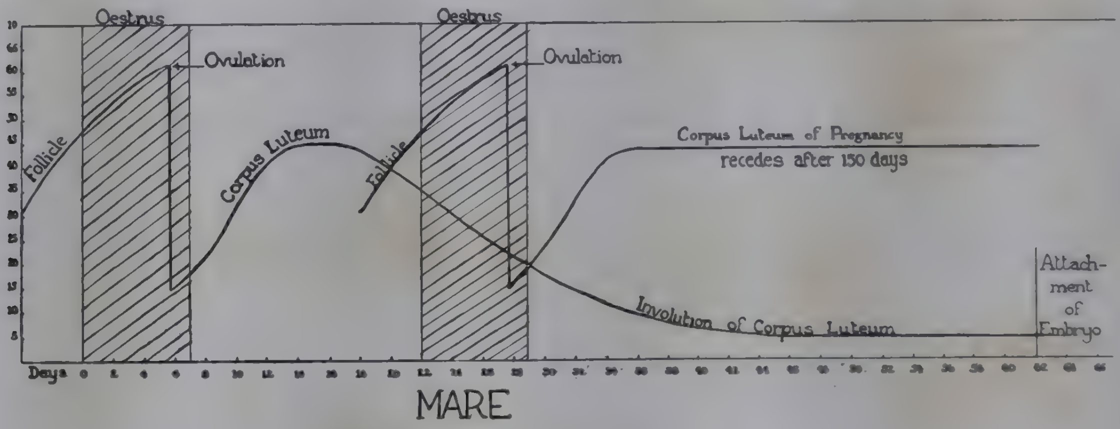

Fig. 176.—The ovarian cycle in the mare.

The cervix is comparatively straight and free from folds, and the semen is believed to penetrate for a considerable distance at service. In artificial insemination it may be introduced into the cervix for several centimeters.

The duration of pregnancy is very variable, the average being about 336 days. But the average for gestations finishing in May is about 341 days, and the average for those finishing in July is 323 days, according to European figures (Wellmann), while the difference in Great Britain is even greater. Thoroughbreds have a longer gestation period than the draft breeds. A mare carrying a mule foal has a longer pregnancy than if she is in foal by a horse. As a biological index of pregnancy the presence of equine gonadotrophins in the blood serum from the 50th to the 145th day may be used, and the presence of estrogens in the urine from the 70th day onward may also be relied upon.

The mare has considerable difficulty in carrying twins to term. In most twin conceptions one of the embryos dies and, although such conceptions are by no means rare, twin births are uncommon.

The mare, and probably also the ass, is peculiar in that the corpora lutea degenerate early in pregnancy, at about the time that chorionic gonadotrophin appears in the blood. This substance causes the ovaries to become active; new ovulations may occur, and, whether they do so or not, new corpora lutea appear. These remain as long as gonadotrophin is found in the blood. When it disappears, the corpora lutea degenerate and the ovaries are inactive for the remainder of the pregnancy. Also, when gonadotrophin is present, the testes or ovaries of the foal increase greatly in size, only to return to the normal size for the fetus when the hormone vanishes from the blood. The significance of these changes is unknown. The time relationships of these changes are given in Fig. 177.

The Cow. The cow comes in heat throughout the year. The first heat period occurs at 4 to 8 months of age, depending on the degree of growth and on the breed. The interval between heats is about 21 days with a normal variation of 18 to 24 days. The duration of heat is very variable, and is, on the average, about 10 hours in heifers and 14 hours in cows. It tends to be shorter and more difficult to detect in winter. The symptoms of heat are restlessness, a tendency to mount and be mounted by other cows, and a slight swelling of the vulva with a flow of mucus.

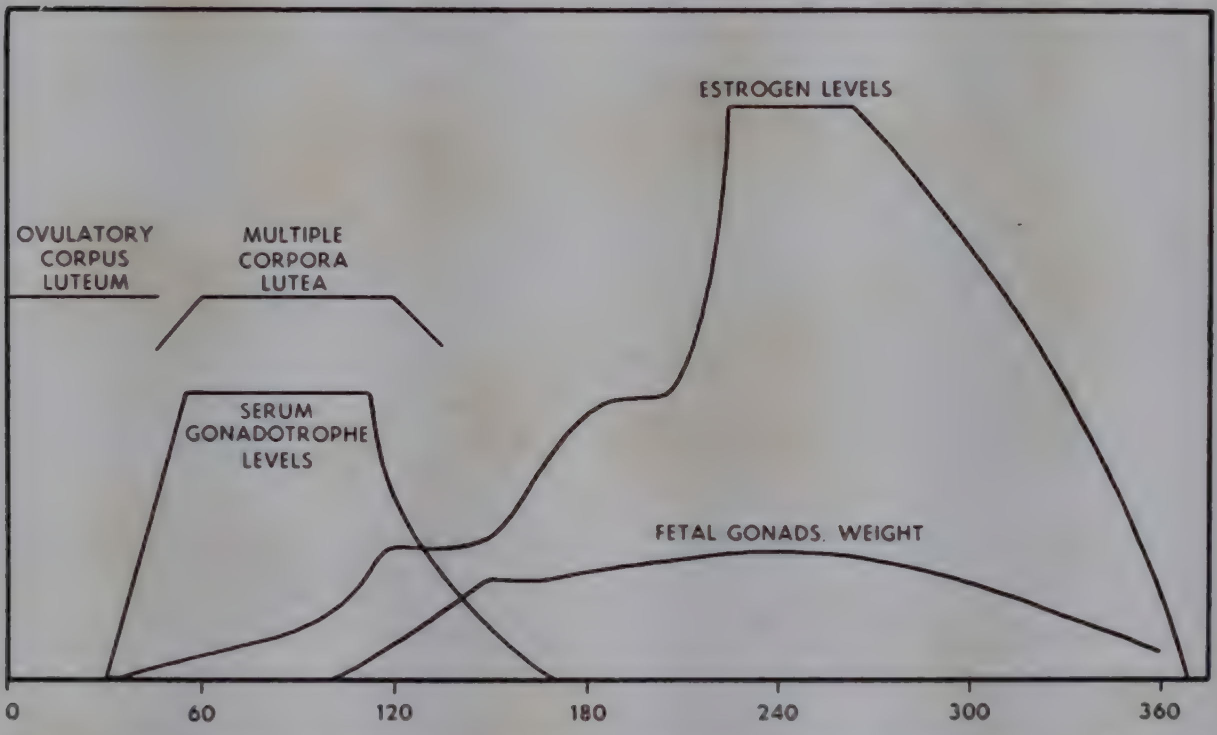

FIG. 177.—Diagram of events during gestation in the mare. (From Asdell, *Patterns of Mammalian Reproduction*, Comstock Publishing Company, Inc.)

Ovarian follicles develop to their greatest size during the latter half of the cycle. One to five follicles normally develop to their maximum size during heat. Ovulation takes place about 14 hours after the animal is out of heat, that is, on the first day of metestrum, and the follicles rupture when from 10 to 20 mm. in diameter. Usually only one of the follicles ruptures, sometimes two, and rarely three. Here again, as in the mare, the ovaries do not invariably alternate in function. The right one functions with slightly greater frequency than the left. At the time of ovulation or just before this, the other large follicles that do not rupture become atretic, lose their tension, and are quickly resorbed. Ovarian follicles in the cow usually lie near the surface. On rectal palpation they are detected as raised areas, quite tense, but they fluctuate freely on digital palpation. If the follicle is not tense, it is atretic and will soon disappear, or else it is pathological.

Hemorrhage into the follicle following ovulation is not the rule. A small amount of fluid is usually found. This is resorbed as the corpus luteum develops, but if an appreciable quantity of sanguineous fluid is formed, it is not readily resorbed, a connective tissue wall is formed around it, and the corpus luteum develops outside this wall, producing what is known as a cystic corpus luteum. The corpus luteum undergoes quite a definite color change during its various stages of life. During the first few days it is a light brown, gradually changing to an old gold and golden yellow at the height of its development. During proestrum it changes to an orange color and gradually deepens in color as the next cycle comes on until it is finally a bright brick-red (the corpus rubrum).

The uterine epithelium reaches its greatest height during proestrum, when it is tall, columnar, and pseudostratified. At estrus it becomes vacuolated, and during metestrum is gradually reduced in height. Marked congestion, edema, and leucocytic infiltration take place in the corium in proestrum, reaching a maximum about the third day of the cycle, and then gradually subsiding. During proestrum and estrus the mucous membrane appears clear, swollen, and gelatinous because of the edema and congestion present. At estrus a small amount of serous fluid is found in the lumen. Ovulation seems to produce a circulatory upset, as both subserous and subepithelial hemorrhages almost invariably follow. The subepithelial hemorrhages break into the lumen of the uterus (second day of metestrum) causing the serous fluid here to become mixed with blood coagulum and strands of epithelial cells. This uterine content passes out through the cervix, causing the flow at this time to be tinged with blood. Cole reports that the uterine glands develop to a marked degree during early diestrum and then regress.

Mucus-secreting cells are found throughout the epithelium of the upper part of the vagina but are more numerous as the cervix is approached. The epithelium of the vestibule is many-layered (stratified).

It decreases in height in the vagina proper, and as the cervical end of the organ is reached it becomes very low (only a few cells deep), the surface layer of cells being mucus-secreting. The epithelium of the vagina and vestibule increases in thickness (layers of cells) during proestrum. The mucus-secreting cells, particularly in the anterior part of the vagina, build up during late diestrum and proestrum and add to the copious cervical discharge of mucus during heat. There is an exudation of lymph through the highly congested corium of the vagina at the time of heat, which mixes with the mucus and makes it thin and watery in consistency. The secretions at this time are less alkaline than during other parts of the cycle; thus the cervical seal liquefies and flows away. Leucocytes invade the vaginal corium in great numbers at estrus and gradually pass through the epithelium into the lumen so that they are most abundant in the metestrous smear. At the junction of the vagina and vestibule is found a rich plexus of veins. This becomes highly congested at the time of heat and so imparts a reddish color to the mucous membrane. The color gradually darkens during metestrum and fades somewhat at diestrum, but there is some color in the posterior part of the vagina at all times of the cycle. The anterior part, when examined with the vaginal speculum appears white and shining during proestrum because of the loaded state of the mucous cells. At heat, mucus is pouring over the surface, and a few injected blood vessels are seen, but these never impart any decided color such as is found in the posterior part of the vagina. During the middle of the cycle the passage appears rather dull and dry, and a small amount of rather heavy, both cohesive and adhesive mucus is found in the lumen of the vagina. If an attempt is made to pass a speculum, it will be accomplished with difficulty due to friction with the dry walls of the organ. In pregnancy the vaginal epithelium is low (only a few cells thick), and it is in places simple columnar.

The duration of pregnancy averages about 282 days, but breed differences are rather great, the average varying from 278 days in Holsteins to 290 days in the Brown Swiss. The bull calf is carried slightly longer than the heifer calf. During pregnancy the cervical seal increases and is almost rubberlike in consistency. Estrogens may be detected in the urine from the 70th day onward. If abortion takes place before the fifth month in the lactating cow no increase in milk yield may be expected, but if it occurs after the fifth month the yield increases. This increase becomes greater in proportion to the length of the interrupted pregnancy. The cow usually comes in heat 3 to 10 weeks after parturition. The interval appears to be longer when the calf is suckled than when the cow is milked.

The ovarian, endometrial, and vaginal cycles in the cow are shown diagrammatically in Fig. 178.

The cow has the lowest sex-hormone output and requirement of all the domestic animals. Injections of estradiol benzoate into ovariectomized cows shows that an average daily dose of 600 rat units for three days causes them to become sexually receptive, but, even though the injections are continued, they remain in heat for less than a day, that is, for the normal time. Evidently in the normal cow the threshold of estrogen at which heat is reached occurs early in the growth period of the follicle. The central nervous system then becomes refractory and the cow then goes out of heat, before the follicle has reached the stage of growth necessary for ovulation. Thus there is an interval of about 13½ hours between the end of heat and ovulation. In all other species whose behavior is known, except for certain bats, the end of heat is caused by the rupture of the follicle and the end of estrogen secretion. The large amount of mucus produced by the cells of the vaginal epithelium at the time of heat is also related to the low estrogen secretion, since if the level is raised by injections less mucin is secreted.

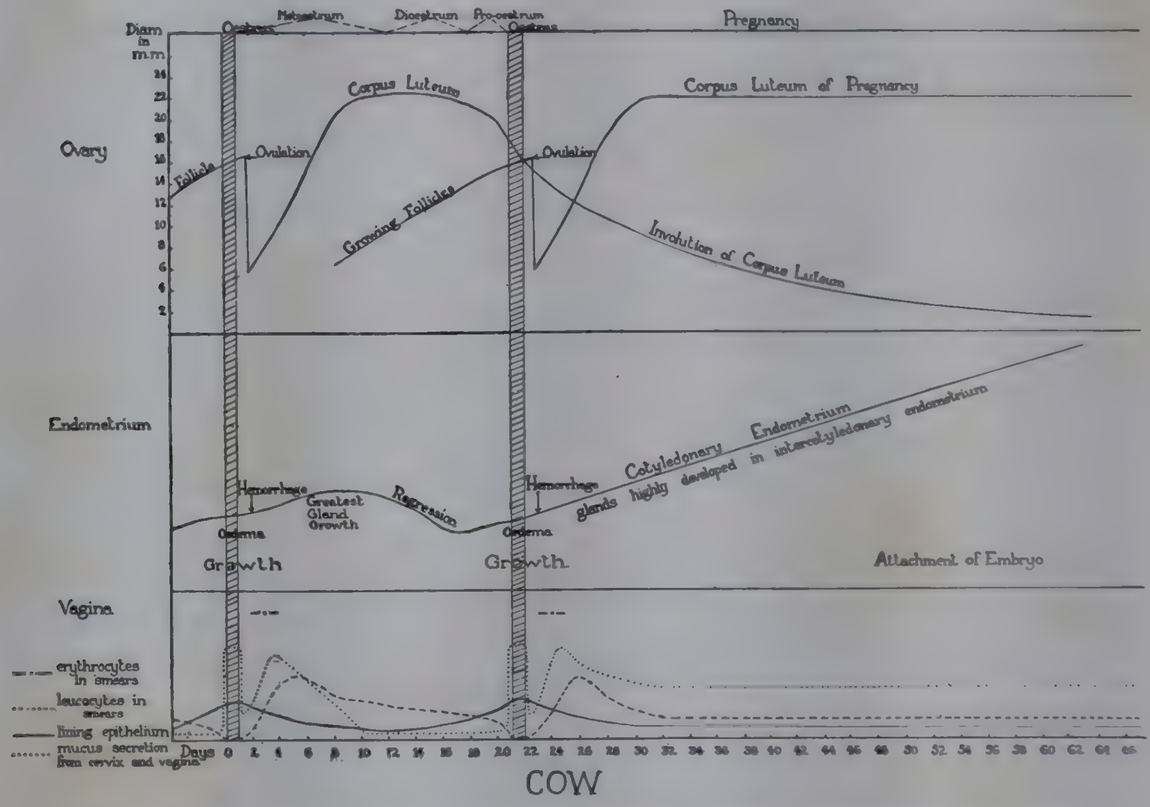

FIG. 178.—The ovarian, endometrial, and vaginal cycles in the cow.

The progesterone requirement is also low. Experimental work has shown that the quiescent state of the uterine muscle, typical of diestrum, is produced by the injection of 35 rabbit units daily. The uterine muscle of the cow responds to adrenaline by relaxation if it is under the influence of estrogens, and by contraction if progesterone is active, a peculiarity shared by the cat and the dog. In proestrum a diphasic response is given, showing that both hormones are active at that time. The diphasic response is given in the ovariectomized cow if 250 rat units of estrogen together with 18½ rabbit units of progesterone are injected, some indication of the hormone levels which are present in proestrum.

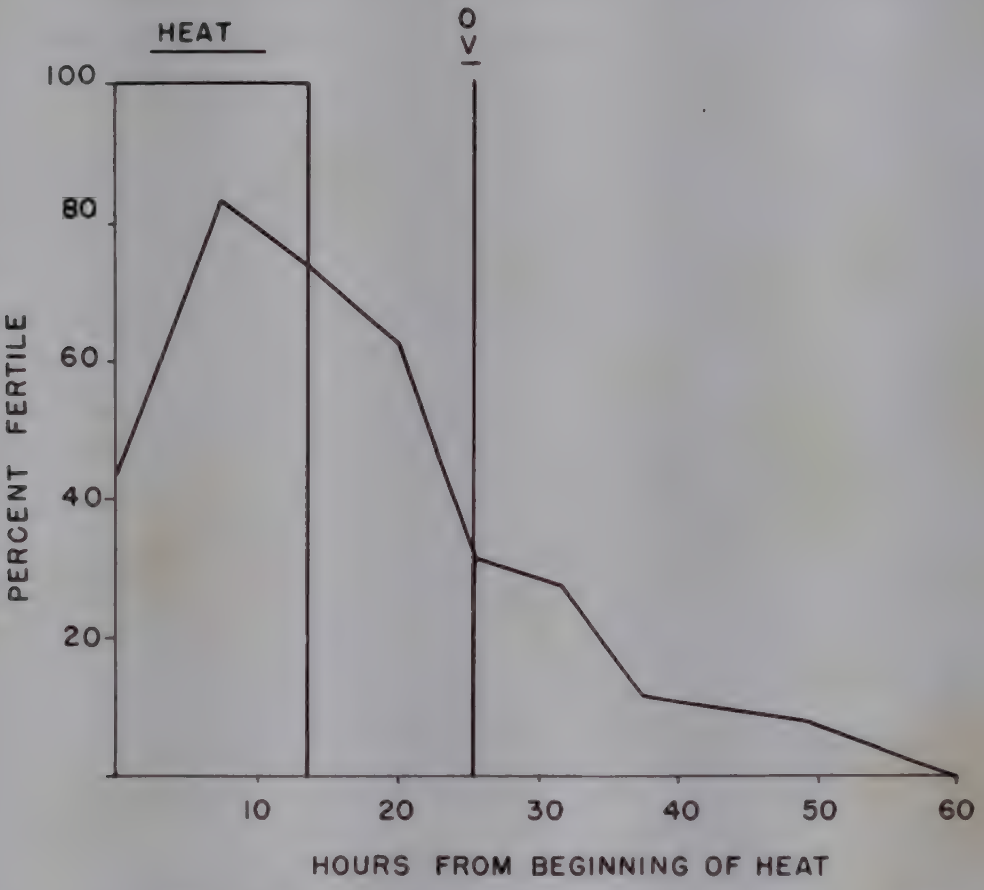

Fig. 179.—The effect of the time of insemination upon the chance of conception in the cow. The duration of heat and the time of ovulation (OV) are shown. (Data from Asdell, *Patterns of Mammalian Reproduction,* Comstock Publishing Company, Inc.)

The chance of conception by a service early in heat is about 44 per cent; this rises to 82 per cent at mid-heat and it remains near this level until 6 hours after heat has ended. Then it falls rapidly until 36 hours after heat, when insemination is practically without result (Fig. 179).

The Ewe. The ewe has a definite breeding season in the early fall. If she is unbred it extends to the latter part of December or a little beyond, but in the Merino and Dorset Horn breeds heat periods may occur at any time of the year. In the southern hemisphere the ewe and the mare experience the breeding seasons at the appropriate season of the year; but, as the seasons are reversed, animals transferred from the one hemisphere to the other need a period of adjustment to accustom themselves to the new conditions. In California breeding occurs rather earlier than in other parts of the United States (Cole and Miller). In South Africa Quinlan and Maré have found that the date of breeding is much affected by nutritional factors. Lambs breed rather later than mature ewes. The average duration of heat is 35 hours and the average interval 16½ days. The eggs are shed about the time the ewe goes out of heat. There is very little vascularization or swelling of the external genitalia when the ewe is in heat (Clark). From one to three follicles rupture at each heat period. The time of mating within the heat period has little effect on fertility.

The proestrous vaginal smear contains thick mucus, leucocytes, and epithelial cells. The presence of mucus and an increased number of leucocytes differentiates it from the diestrous smear. As estrus develops the smear becomes more fluid, leucocytes decrease, and squamous epithelial cells appear. During metestrum the smear becomes voluminous and cheesy, and it contains an abundance of squamous epithelial cells with but few leucocytes. Cornification is much more marked than in the cow (Cole and Miller). It may be noted that this type of smear, characteristic of estrus in many other species, appears later in the sheep. The changes in the vaginal epithelium, though following the usual cycle, are less marked than one would expect from the smears.

During proestrum and estrus the endometrium is edematous and the surface is composed of high columnar cells. These are also found in the bases of the glands during metestrum and into early diestrum. The glands develop considerably at this time. During anestrum marked regression of the endometrium and glands occurs. During the early part of this period also, waves of graafian follicles grow in the ovaries but they do not reach ovulation point. This suggests that rhythmic impulses are still at work, even though the corpora lutea are not formed, but that the impulse, probably anterior pituitary hormone, is not sufficient to cause ovulation.

The duration of gestation is about 150 days, but may vary from 140 to 160 days. Usually the early-maturing meat breeds have a shorter gestation than the later-maturing wool breeds.

Cole and Miller have found it possible to bring ewes into heat and to breed them during anestrum by two injections of anterior pituitary hormone with a 16½-day interval between injections. This is the normal interval between heats. But the results of these injections have not been uniformly successful and there is some evidence that small growing follicles must be present in the ovaries at the time the injections are made. This condition is fulfilled late in anestrum, and ovulations without heat may occur as a result of the first injection. Hammond and coworkers believe that for both ovulation and heat it is necessary that a corpus luteum be present in the ovary, a condition which is met at the second injection. The problem needs further work before the mechanism is fully understood. Attempts to bring ewes in heat earlier than usual by exposing them to smaller amounts of light during the summer months have given inconclusive results.

The Goat. The estrous cycle of the goat is essentially similar to that of the ewe but the duration of estrus is about half a day longer, while the interval between heats is about three days longer. Gestation averages a day more. The number of graafian follicles maturing at one time varies from 1 to 5.

Only one injection of gonadotrophin late in anestrum seems to be necessary to bring does in heat and to cause ovulation. Exposure of does to smaller amounts of light than usual in late spring has led to much earlier breeding and pregnancy than is normally the case.

The Sow. The sow has a long breeding season probably extending over the whole year except when she is pregnant or suckling. The duration of heat is from 1 to 5 days, with 2 to 3 as the average. The interval between heats varies from 18 to 24 days, with 21 as the average. Puberty is reached at 3 to 5 months of age under normal conditions of husbandry.

After ovulation, which usually occurs on the second day of estrus, only small ovarian follicles are found. The number of small follicles found during metestrum and diestrum would probably average twenty or so in each ovary. Most of these grow gradually until proestrum to a diameter of four to six millimeters. During proestrum they increase to a diameter of eight to twelve millimeters. As estrus is reached there are fifteen to forty large follicles in the ovaries, practically all of which rupture at ovulation time. McKenzie reports that the weight of the ovary varies from 3.5 to 10 gm., being lightest following ovulation and heaviest during the diestrous period when the corpora lutea are fully developed. The corpora lutea are pinkish when fully developed but become pale primrose-yellow as degeneration sets in. At this time their vascularity is greatly reduced, which accounts for their change in color. Hemorrhage rarely occurs into the cavity of the ruptured follicle, but graafian follicles with internal hemorrhages are frequent. The ovarian cycle in the sow is shown diagrammatically in Fig. 180.

The epithelium of the uterus is simple columnar, with cilia appearing in the gland crypts but not on the surface. The epithelium grows to a tall, columnar, and pseudostratified type at proestrum, and remains so for about one week of the next cycle. Vacuolar degeneration takes place, and the epithelium is reduced again to a low columnar type at diestrum. Leucocytes appear quite numerous during proestrum and estrus, and then disappear gradually throughout the first week of the new cycle. The usual proestrous and estrous congestion of the corium is also characteristic of the sow, but gland development during metestrum has not been reported.

The vagina contains no mucus-secreting cells, and the amount of mucus in the flow is decidedly less than is found in the cow. The epithelium of the vestibule and vagina reaches its lowest point at the end of metestrum. It immediately starts to build up again and reaches its greatest thickness at estrus. At this time leucocytic infiltration of the mucous membrane is marked, the leucocytes passing into the lumen and appearing in the discharge during late estrus and early metestrum. The epithelium never becomes truly cornified and starts desquamating at the time of estrus, continuing through metestrum. The greatest mucus discharge occurs during estrus, at which time the external genitalia are swollen, congested, and pinkish in color, and the membranes are quite moist. In late estrus and early metestrum a whitish discharge not infrequently collects on the vulva, often spoken of as whites. It consists of mucus and of cellular material, the latter of which includes large numbers of leucocytes. They usually appear abundantly in the smear in metestrum and are practically absent during estrus. Epithelial cells are found most abundantly in early metestrum but appear throughout the cycle. No especial cornified stage is attained at any time. Erythrocytes do not appear in the smear from the sow. The vaginal smear in the sow does not seem to be a very satisfactory means of determining the various stages of the cycle.

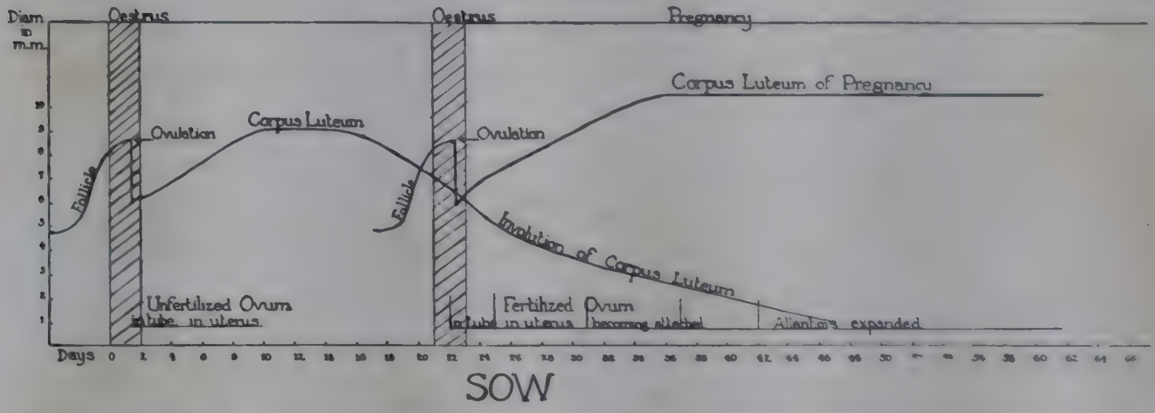

FIG. 180.—The ovarian cycle in the sow. (Slightly modified from Corner.)

The duration of pregnancy is 113 days, but a variation of about 3 days on either side may be regarded as normal.

The Dog. The bitch usually has two breeding seasons in the year, in the spring and the fall, but individuals of the smaller breeds may have three. The proestrous period lasts about a week, and is characterized by a marked swelling of the vulva and a clear sanguinary discharge. This period passes insensibly into the heat period proper, which also lasts about a week.

Evans and Cole state that the number of medium-sized follicles in the dog's ovary reaches its height at the incidence of proestrum. They claim that the number of small and medium-sized follicles is greatly reduced during proestrum as a result of marked atresia. However, those follicles destined to ovulate continue to develop. A remarkable feature by which the dog differs from other animals studied is in the fact that the membrana granulosa and inner theca are thrown into marked folds before ovulation. Follicles may reach a size of 10 mm. in large dogs at the incidence of ovulation, which occurs on the first or second day of estrus. The number of follicles rupturing in the bitch at one estrous period varies with the size of the dog and with the breed. It may be as low as four in some of the smaller breeds and as high as twenty or more in the larger ones. The egg of the bitch is remarkable for the fact that at ovulation the first polar body has not been extruded. The egg is therefore not mature and cannot be fertilized for a few days, until the polar body is shed.

There is a redistention of the ovarian follicle following ovulation, the developing corpus luteum gradually displacing the fluid. The corpus luteum becomes solid toward the end of estrus or early metestrum. It remains fully developed for about 30 days and then shows cellular degeneration; it involutes slowly and can still be seen in a badly degenerated form when the next cycle begins six months later (see Fig. 181).

It is to be expected that the dog, having but two estrous cycles per year, would vary markedly from the polyestrous animals just described. Evans and Cole give the average proestrous period as 9 days; estrus, 9 days; and metestrum, nearly 3 months. They describe as metestrum the combined periods which in polyestrous animals would be called metestrum and diestrum. The three-month period is consumed in the developmental and regressive uterine changes known as pseudopregnancy (progestational stage—Corner).

Throughout anestrum, which lasts about two months, the uterine mucous membrane is shallow, the epithelium is low cuboidal, and the glands and their crypts are but poorly developed. At proestrum and continuing through the first part of estrus, there is a marked congestion and edema of the corium but very little change in the epithelial elements. Hemorrhages take place at proestrum, with the escape of blood into the lumen of the uterus. This blood is responsible for the sanguineous nature of the proestrous discharge. On the sixth day of estrus the epithelium shows marked activity, the surface epithelium is higher, the crypts become well developed, and there is a decided increase in the glandular development and complexity. The glandular complexity remains until about the twentieth day of diestrum, when involutionary changes set in. These continue to about the ninetieth day, when the organs pass into the anestrous stage. It will be noted that the development of the uterine glands is coincident with the development of the corpora lutea in the ovaries, no marked development of uterine glands taking place until the corpora have developed far enough to be considered functional.

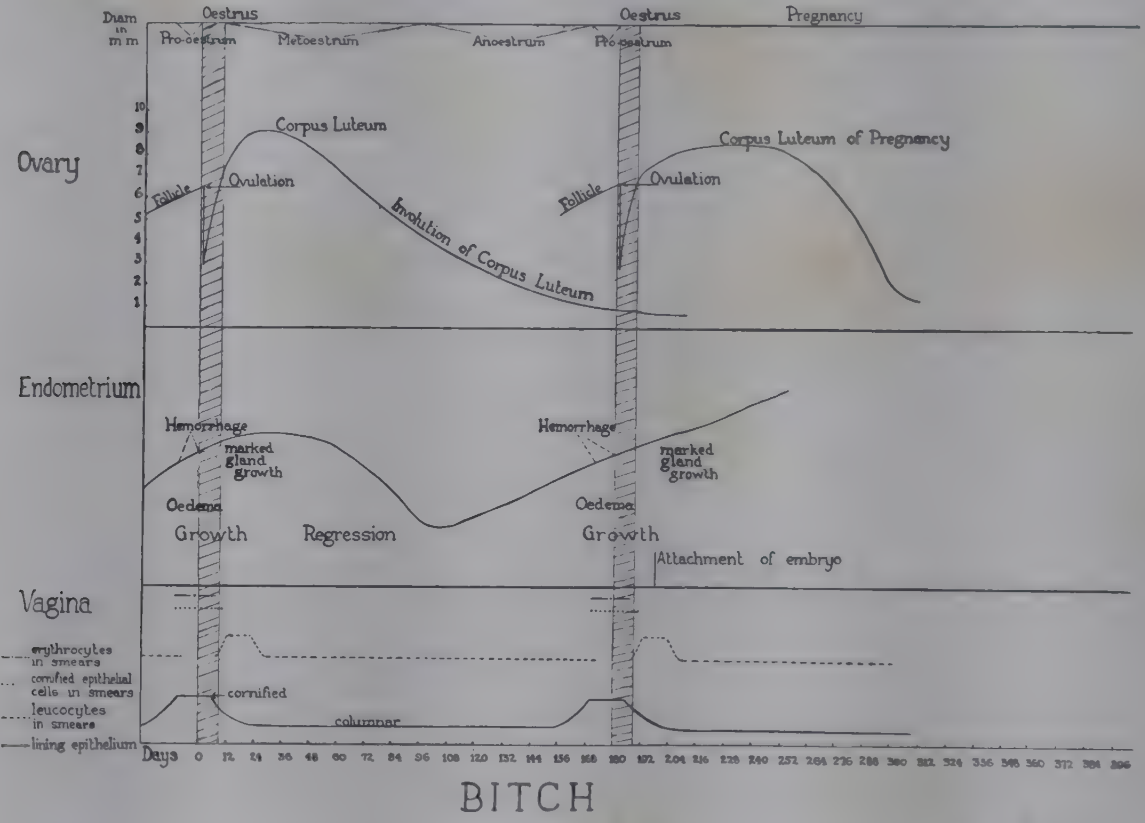

FIG. 181.—The ovarian, endometrial, and vaginal cycles in the bitch.

The vaginal epithelium at anestrum consists of two or three layers of cuboidal or columnar cells (Fig. 173, p. 739). The epithelium gradually builds up until at proestrum and estrus it is a high stratified squamous epithelium with a superficial stratum corneum (Fig. 174, p. 740). By the end of estrus the cornified layer of cells is lost through desquamation, and the epithelium gradually returns to a columnar type at about the third week of metestrum.

The external genitals of the bitch become markedly swollen and enlarged during proestrum and estrus. At the beginning of proestrum there is a blood-stained fluid discharge from the vulva, which persists through early estrus. The vaginal smear shows noncornified epithelial cells and leucocytes throughout metestrum and anestrum. At proestrum erythrocytes and cornified epithelial cells are added to this picture and leucocytes are lost. During late proestrum and estrus only red blood cells and cornified epithelium constitute the smear. The approach of metestrum is heralded by the presence again of leucocytes and the gradual loss of cornified cells.

The duration of pregnancy is about 60 days.

The Fox. The fox in captivity has one breeding season each year, in February or March. This monestrous cycle seems to be essentially similar to that of the dog, but, as the estrous period does not last so long and the discharge of blood during proestrum is less, the intensity of the changes which occur in the tubular genitalia is probably less. The gestation period is shorter than in the dog, being about 52 days.

Matings made on the first day of heat are considerably less fertile than are those made on the second and third days.

The Cat. The cat is seasonally polyestrous and may experience two or more seasons during the year. She remains in heat for about 4 days at a time. Ovulation is not spontaneous but requires the stimulus of coitus to produce it. It occurs 26 to 27 hours after coitus. The eggs take 5 days to reach the uterus. Gestation lasts about 63 days. After the 49th day the corpus luteum is no longer essential for gestation. The vaginal and uterine reactions during the cycle are clear-cut and follow the usual sequence (Gros).

The Fowl. The ovary of the fowl contains a large number of ova, a few of which are growing at any one time. A period of slow growth occurs until they are 6 mm. in diameter. Then a period of rapid growth sets in at an average rate of about 4 mm. in diameter each day for about eight days, though it becomes less as the time of ovulation approaches (Warren and Conrad). The fully grown ovum is about 4 cm. in diameter. The growth consists of an increase in the yolk which is deposited in concentric layers. The nucleus or germ spot lies on the periphery of the yolk sphere, beneath the vitelline membrane. The color of the yolk varies with the amount of xanthophyll in the feed and may be changed at will.

Ovulation occurs by the rupture of the follicle along a streak called the stigma. Rupture is probably due to internal pressure caused by the formation of the yolk and to prolonged tension of the muscle fibers. In a laying hen it usually occurs about half an hour after an egg is laid, but no causal relationship is known to exist between the two events. Ovulation is most frequent between 5 A.M. and 2 P.M. No corpus luteum is formed in the empty follicle. Passage of the egg down the oviduct is made possible by peristalsis, probably aided to some extent by ciliary action. During its passage the ovum is surrounded by four layers of albumen. This is mainly deposited in the magnum or ovarian end of the oviduct. It is secreted in very concentrated form; but as the egg proceeds down the oviduct, water is absorbed so that the albumen is diluted and the egg increased in size. The albuminous coats are surrounded by two "shell membranes" which are deposited as the egg passes through the isthmus of the oviduct. The last part of the oviduct is the uterus, in which the egg acquires its shell, or coating of calcium carbonate. The shell is a porous coat consisting of two layers and a cuticle. Besides $CaCO_3$, the shell contains 1 per cent of $MgCO_3$, 1 per cent of $Ca_3(PO_4)_2$, and 4 per cent of protein. The egg passes through the magnum and the isthmus in about 4 hours, and through the uterus in about 21 hours. Thence it passes through the vagina, and it is expelled by eversion of the cloaca. The laying process takes but a few minutes. About 70 to 90 per cent of the eggs are laid small end first. The shape appears to be due to the action of mechanical factors.

The intervals between layings are usually a little more than 24 hours, so that successive eggs are laid later each day. When a hen becomes due to lay an egg after the middle of the afternoon, a delay usually occurs until the following morning, when a new series of daily layings is started. The delay is caused by a temporary lengthening of the interval between ovulations and not by the retention of an egg (Warren and Scott). The age at which the first egg is laid varies with the breed. In Leghorns it is at about 200 days.

The number of eggs laid each month closely follows the length-of-daylight curve throughout the year. Increase of light during the darker months increases the number of eggs laid. This was believed to be due to the greater amount of time available for feeding. However, a gradual increase in the duration of light is more effective than a sudden sustained increase, so it is now thought that the effect is caused by the stimulating action of light upon the anterior pituitary. Light is known to stimulate this gland in the duck and in some migratory birds, but no experiments designed to test the effect of light upon the anterior pituitary of the fowl, or even of the anterior pituitary upon the rate of ovulation, have yet yielded convincing results.

It takes 2 to 3 hours after copulation for the first spermatozoa to reach the ovary. Fertilization occurs immediately after the egg is shed if spermatozoa are present, not, as was formerly supposed, within the ovary. The spermatozoa retain their full fertility for 6 days after they are deposited within the female, in marked contrast to the much shorter time in mammals. At the tenth day only 50 per cent of the eggs laid are fertilized, and by the 19th day only 15 per cent; though occasional eggs may be fertilized up to 26 days after a single insemination.

Hormonal Activity in the Fowl. The growth of the oviduct is under the influence of estrogenic hormones, just as it is in mammals, while the development of the ovary is under the influence of pituitary gonadotrophe. Why in nonpredatory birds the left ovary alone develops is unknown.

Broodiness, or the instinct to sit upon the eggs and hatch them, is under the influence of the anterior pituitary hormone prolactin, which is produced by the fowl although no mammary glands are present upon which it may take effect. Molting is under the influence of the thyroid, and it may readily be induced by the injection of thyroxine or of thyrotrophic hormone.

The effects of male and female hormones upon the secondary sex characters have already been mentioned (p. 745). Occasionally the functional left ovary of fowls is destroyed or damaged by tumor formation or by tuberculosis. Under these conditions the rudimentary right gonad develops, either as a testis or as a dual organ, an ovotestis. In these birds male and female characters develop side by side. The large comb and the crowing voice of the male may be present with the special plumage of the female. Frequently the trend is first toward complete maleness, even of plumage, which indicates that estrogens are not being formed, but only androgens (testicular hormones). This may be followed by the male comb and voice with female plumage because of the formation of both types of hormones. The embryological basis for sex reversal is found in the fact that in the female two ingrowths of sex cords into the rudimentary gonad occur. The primary, or medullary, cords are testis-forming, and the secondary, or cortical, cords are ovary-forming. If the function of the cortical cords is disturbed, the medullary cords which have been suppressed are able to develop as testicular tissue and to produce their characteristic hormone. Occasionally even spermatogenesis may take place in such a sex-reversed bird. The opposite change, from male to female, is exceedingly rare, and a satisfactory explanation for such a change has not yet been found.

INTERSEXES

Occasionally our attention is drawn to anomalies of various types in the sexual apparatus. In cattle these usually occur among twins. The freemartin, or the calf with female external genitalia, co-twin to a bull, is, in 9 cases of 10, sterile. The bull calf is usually fertile. Statistical analysis of the incidence of sex in twin calves strongly suggests that the freemartin is genetically a female. Embryological research has shown that there is an anastomosis of the blood vessels of the chorion in these twins. Normally the testis develops a little before the ovary. The gonads of the female twin are believed to be affected by the earlier-produced male hormone, which passes across into her circulation so that they develop as abortive testes, while the female tubular genitalia are partly suppressed and the corresponding male structures partly develop (Lillie, Tandler).

Other types of intersexes are found in all classes of animals, but most frequently in the pig, goat, and man. They may be classified into two main types. The first type, which is by far the rarer, possesses ovary and testis or compound organs described as ovotestes. The tubular genitalia in these animals usually consists of both male and female structures more or less fully developed. The external genitalia are usually distinctly female, but the clitoris is enlarged and prominent. In the second type, pseudohermaphrodites, the only gonadal tissue is testicular, while the accessory organs are variable. In some the external genitalia are female, but the clitoris has enlarged under the influence of the male hormone, and the tubular genitalia of both sexes have usually developed. In others the tubular genitalia are male while the penis has failed to grow to the usual extent. The sheath has failed to grow and often does not unite in the midline so that the penis is pendent and the urethral canal may become distended during urination. Sex ratio data indicated that goat pseudohermaphrodites are genetic females, but in man they are genetic males.

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Chapter XL

THE MALE GENERATIVE ORGANS

THE age at which gametogenesis first appears and the secondary sex characteristics develop is somewhat later in the male than in the female. While complete sexual development consumes considerable time in both the male and female, yet the male is much slower in the completion of the sexual changes. Some males, particularly those of the wild species, such as deer, exhibit a definite season of sexual excitement known as rut. This male sexual season is also exhibited by the camel and elephant. Spermatogenesis occurs only during this period. At other seasons of the year the testicles are in an inactive condition and in some species are greatly reduced in size. In several animals that hibernate in the winter, such as the hedgehog, the testicles as well as the accessory sexual glands become markedly enlarged in the spring. There is also a remarkable increase in interstitial tissue in the testicle. In the common domestic mammals, however, there is no definite breeding season for the male. Spermatogenesis is a continuous process, and the male is ready for coitus at any time.

In birds the testicles enlarge to several times their former size and weight during the spring and early summer, which constitute the breeding season. This is also true of the domestic fowl. In migratory birds the genital organs increase greatly in size in both sexes as the spring period of migration is approached. This is thought to be one of the primary causes of migration. When the birds are ready to migrate again to their winter quarters, the genitals atrophy and assume a quiescent state. It has recently been shown that these growth effects can be produced experimentally by increasing the light ration by strong electric light. They are therefore probably caused by changes in the length of the day.

The male generative organs consist of the main sex gland or testicle, the accessory sexual glands, the copulatory organ or penis, and the conducting tubes. The accessory sexual glands include the ampulla of the ductus deferens, the seminal vesicles, the prostate, and the bulbo-urethral glands. These are all paired glands except the prostate, which is single. Not all males possess all the accessory sexual glands;

the number present varies with the species of mammal. The stallion, jack, and bull possess all the accessory glands; in the boar the ampulla of the ductus deferens is absent; in the dog the seminal vesicles and bulbo-urethral glands are absent; the cat lacks the seminal vesicles. The conducting tubes consist of the efferent testicular ducts, the epididymis, the ductus deferens, and the male urethra. The testicular ducts are six to twenty-four in number and they soon unite, upon leaving the testicle, into one duct, which constitutes the origin of the epididymis. The urethra consists of the pelvic and extrapelvic parts, the latter being entirely incorporated within the penis. It is into the pelvic urethra that the sexual glands discharge their secretions.

THE TESTICLE

In most domestic mammals the testicles are located in a diverticulum of the abdominal cavity, the scrotum. In rodents and insectivores the testicles are in the abdominal cavity except during the breeding season, when they descend to the scrotum. In some of the lower orders of mammals there is no scrotum, the testicles remaining in the abdominal cavity. In birds they assume a position in the dorsal part of the body cavity.

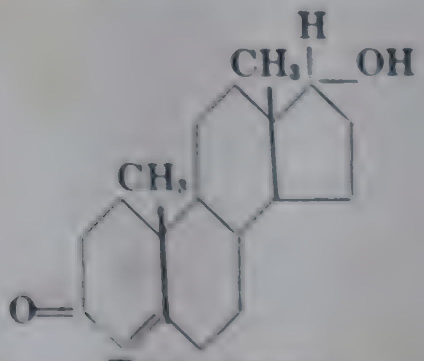
The testicle is covered by peritoneum under which is a dense fibrous capsule, the tunica albuginea. Fine trabeculae are given off from this into the substance of the gland and form a central connective tissue core, the mediastinum testis. No mediastinum, however, is found in Equidae. The glandular elements consist of the convoluted seminiferous tubules, which form the spermatozoa. Between these tubules are found islets of epithelioid connective tissue cells, the interstitial tissue of the testicle. The seminiferous tubules form a rete testis in the mediastinum, when this is present, and from this network emerge the efferent testicular ducts. These soon converge into one tubule in the head of the epididymis. Blood is supplied to the testicle chiefly from the great spermatic artery, although the lesser spermatic and the artery of the epididymis may also supply some blood to it. The great spermatic artery is much coiled just before it reaches the testicle. In the boar this coil may be found to be fifty feet in length if straightened out. The testicle is supplied by nerves derived from the sympathetic system.

The seminiferous tubule consists of several layers of epithelial cells, which by multiplication and maturation produce the spermatozoa. Next to the basement membrane of the tubule is found a layer of cuboidal cells, the spermatogonia. These multiply, and a portion of the new cells push inward to form the primary spermatocytes. By division of the primary spermatocytes, secondary spermatocytes are produced, and the number of chromosomes is reduced to one-half in preparation for union with the egg cell. This union restores the number to the normal for the species. The division of the secondary spermatocyte forms the spermatid. The spermatid elongates, and the nucleus moves to one end, forming the head. In this way spermatozoa are formed. The scheme of maturation of the sperm is seen in Fig. 168, p. 728. The spermatozoa attach themselves to the free end of tall columnar cells, which are known as Sertoli cells. These are attached to the basement membrane and are thought to supply nourishment to the maturing spermatozoa during their development. No blood vessels enter the tubules; they are confined to the intertubular spaces. A fluid is produced in the testicle and in the epididymis; this serves as a medium in which the spermatozoa move and also possibly furnishes nutritive material to them. Spermatozoa are continuously being produced and shed by the seminiferous tubules. The number found in the tubules is lowered following several successive emissions but returns to normal again after a period of rest. Spermatozoa possess motility as a result of the activity of the tail-piece. The rate of movement depends upon the temperature and the vitality of the spermatozoa. They are most active at body temperature, become inactive as the temperature is lowered, and are completely destroyed by higher temperature (47 degrees C.—Young, 1929). The rate of movement of spermatozoa is said to be about 3.6 mm. per minute at body temperature.

The Function of the Scrotum. The temperature of the scrotum is somewhat lower than that of the abdominal cavity. This fact, together with the fact that testicles abnormally retained in the abdominal cavity (cryptorchid) in the adult do not produce spermatozoa, has led to the belief that the scrotum regulates the temperature of the testicles. The seminiferous tubules of testicles experimentally confined in the abdominal cavity of adult guinea pigs show marked degeneration. All spermatogenesis ceases, but the testicle becomes active again in the production of spermatozoa if allowed to re-enter the scrotum. This tends to show that abdominal temperatures are too high for the production of spermatozoa in animals possessing a scrotum. Experimental work also points toward a longer life of the sperm in the epididymis when exposed to the lower scrotal temperature than when exposed to the higher abdominal temperature. Production of the male sex hormone does not seem to be affected by retention of the testicle in the abdominal cavity, since in the cryptorchid the accessory organs and the secondary sexual characters are fully developed.

The Internal Secretions of the Testicle. In the preceding chapter it was shown that ovarian activity is largely governed by the anterior lobe of the pituitary body, and that the ovary, in turn, is largely responsible for the functional state of the remainder of the female reproductive organs. A similar statement holds true for the male reproductive organs. Extracts or transplants of the anterior pituitary lobe do not cause as rapid changes in the immature male organs as is the case in the female; nevertheless, these changes are well marked. The follicle-stimulating hormone is necessary for spermatogenesis, while the luteinizing hormone stimulates the interstitial cells of the testis to secrete their hormone, testosterone.

The Male Sex Hormones. Early castration of the male results in a failure of the secondary male sex characteristics to develop. For a discussion of these characteristics, see the previous chapter. Early castration also results in a failure of the accessory sex glands and penis to reach the state of development found in the normal male. Late castration results in an atrophy of the accessory sex glands. In the capon the comb and wattles fail to develop and the crowing instinct is lost. These changes are due to the removal of the male sex hormone, testosterone, which is elaborated by the testicle. In the female the vaginal smear from the spayed rat, mouse, or guinea pig, showing the absence of leucocytes and the presence of cornified epithelial cells following hormone injection, represents a very definite test for estrogens; and for the male hormones, tests such as the effect on the epithelium of the prostate and seminal vesicles of the castrate are now being used. Probably the most delicate test yet discovered is the growth response of the comb in the capon. The male hormone, testosterone, is a steroid similar in structure to progesterone. It is excreted in the urine as androsterone, a less active form. As a class, hormones which stimulate the male accessory organs are termed androgens. The formula which follows is that of testosterone:



Testosterone

The action of testosterone is greatly enhanced by the presence of fatty acids. Bulls' testes are a good source of the hormone, but it is demonstrated only with great difficulty in the testes of same. Oral administration has been shown to be relatively ineffective; subcutaneous or intravenous injections must be used.

While much has been written concerning antagonism between the male and female sex hormones, Moore and Price present evidence which shows that these hormones are without effect upon each other, but rather that their apparent antagonism is due to their influence upon the pars anterior of the pituitary body. Either of them, whether injected into the same sex or into individuals of the opposite sex, depresses the action of the anterior pituitary on the gonads. This has, in the case of injection into individuals of the opposite sex, led to the suggestion that the hormones are antagonistic, but, as this action takes place regardless of the sex, the inference was incorrect. Furthermore, when the two hormones are injected into capons, testosterone causes male development of the comb and wattles, while estradiol causes development of female feathering. Each hormone acts upon its own specific structures.

THE ACCESSORY SEXUAL ORGANS

The Epididymis. The epididymis is closely related to the testicle. It consists of a head, neck, and tail, which are composed of a single, coiled tubule starting with the union of the vasa efferentia at the head and continuous with the ductus deferens at the other extremity. The tubule is lined by a tall, ciliated, simple columnar epithelium, which is surrounded by connective tissue containing some smooth muscle cells. The tube becomes larger in the tail and contains a better-developed muscle coat. The length of the ductus epididymis varies greatly in the different species of mammals. In the guinea pig, it is 9 to 9½ feet, whereas in a boar possessing large testicles it had an estimated length of over 500 feet. Many theories have been advanced as to the functions of this long, coiled tube, but these still remain only partially known. Young (1931), using spermatozoa from the head and tail parts of the epididymis artificially to inseminate female guinea pigs, found that sperms from the head of the epididymis were 33.3 per cent successful, while those from the tail were 68 per cent successful. Young considers that "the time consumed by spermatozoa in passing through the epididymis is necessary for a completion of their development and that the changes undergone during this period represent a continuation of changes which start while the spermatozoa are still attached to the germinal epithelium, and are not conditioned by some specific action of the epididymal secretion." Spermatozoa that are not ejaculated, for the most part, disintegrate in the epididymis. The seminal constituents of the epididymis have a milky appearance and they consist of a fluid secretion from the testicle and epididymis in addition to spermatozoa. Spermatozoa are inactive while in the testicle, but a mild activity is noticed in spermatozoa from the epididymis. Spermatozoa in the epididymis remain capable of fertilizing ova for several days. It is probable that the epithelium of the epididymis furnishes some food to the spermatozoa as glycogen has been found in the epithelium.

The Ductus Deferens. The ductus deferens is primarily a conducting tube for the seminal fluid from the epididymis to the pelvic urethra. It contains a well-developed smooth muscle coat, which is instrumental in the conveyance of a seminal fluid during ejaculations. Some claim that peristaltic movements occur; others that sudden contractions suffice to eject the fluid, and that true peristalsis does not take place. The ampulla of the ductus deferens varies greatly in size in different species. It is absent in the boar, small in the dog and cat, and well developed in Equidae, the bull, and the ram. It is very large in the jack, in which it may measure 1¼ inches in diameter and 6 inches or more in length. It contains glands that open into the ductus deferens and add to the fluid portion of the semen. Sympathetic fibers from the second to the fourth lumbar nerves pass through the posterior mesenteric ganglion and are distributed to the internal genital organs through the hypogastric nerve. Contraction of the musculature of the ductus deferens can be produced by stimulation of either the lumbar radicles or the hypogastric nerve.

The Seminal Vesicles. Seminal vesicles are not present in the dog and cat. They consist of true vesicular structures with glandular walls in Equidae, and are still more developed in the bull, ram, and boar. In the boar they reach a remarkable size. The secretion of the seminal vesicles enters the urethra with that of the ductus deferens by means of the ejaculatory duct. The quantity, character, and importance of the secretion, must, of necessity, vary with the species of animal. In the guinea pig and rat the secretion of the seminal vesicles is coagulated by coming in contact with the secretion of a portion of the prostate, known as the "coagulating gland." This coagulum produces a plug in the vagina of rodents, which prevents the escape of the semen and furnishes an aid to fertilization. Removal of the prostate and seminal vesicles in laboratory rodents results in diminished fertility. The secretion of the seminal vesicles of most animals is a white or yellowish-white gelatinous fluid. It is said in man to consist largely of globulins.

The Prostate Gland. The prostate gland, to a greater or lesser degree depending upon the species, surrounds the pelvic urethra. In many species it extends along the dorsum of the urethra for some distance, covered by the urethral muscle. It is an unpaired gland but possesses two rows of openings, one on each side of the ejaculatory ducts, through which openings its secretion empties into the urethra. The prostatic secretion is an opaque liquid having a neutral reaction and a characteristic odor, which is, in a large measure, responsible for the odor of semen. Spermatozoa have long been known to become more active in the presence of prostatic secretion, but this is now thought to be due to the removal of carbon dioxide that has been thrown off by the spermatozoa themselves. Spermatozoa are rendered inactive in an acid medium; thus they tend to limit their own activity by the production of carbon dioxide. The absorption of carbon dioxide by the prostatic secretion causes them to be decidedly active at the time of ejaculation. Secretory nerve fibers to the prostate come from the hypogastric, while motor fibers are received from both the hypogastric and nervi erigentes.

The Bulbo-Urethral Gland. Bulbo-urethral glands are absent in the dog but present in other species of common domestic mammals. They lie on either side of the posterior part of the pelvic urethra, inclosed by the urethral muscle, except in the boar. In this animal they reach remarkable dimensions; they extend almost the entire length of the pelvic floor and may reach a diameter of 1½ inches. The ducts of the bulbo-urethral glands discharge the viscous secretion of the glands into the posterior part of the pelvic urethra. No specific function has been attributed to the secretion of these glands, though it is believed that they may assist in clearing the urethra as a preparation for the passage of spermatozoa. Secretory fibers come from the pudic nerves.

COITION AND INSEMINATION

Erection and Ejaculation. The penis serves the double purpose of expelling the urine and placing the semen in the genital tract of the female. Before the latter function can be executed, it is necessary for the organ to become erect. Erection is admirably provided for by the presence in the penis of three erectile structures: the two corpora cavernosa penis and the corpus cavernosum urethrae. Stimulation of the nervi erigentes results in erection. These nerves are composed of parasympathetic fibers derived from the sacral nerves. Their stimulation causes a dilatation of the vessels supplying the penis (branches of the anterior and posterior pudic, and the obturator arteries). The cavernous blood sinuses of the penis expand, and the outflow of blood is retarded by increasing the venous pressure, probably as a result of contraction of the smooth muscle of the corpora cavernosa themselves and the extrinsic muscles of the penis (ischiocavernosus). If the penis is divided and the nervi erigentes stimulated, blood will flow several times faster from the cut surface than if the organ is left in a quiescent state. The acts of erection and ejaculation are reflex acts, the centers being located in the lumbar portion of the spinal cord. This has been proved by showing that the reflex still takes place after dividing the cord at the thoracolumbar junction. Normally, however, the nervous paths involve the brain. A certain area of the cerebral cortex has been electrically stimulated in the dog, causing erection and emission. Erection may be reflexly stimulated from the testicles, urethra, prostate, or the penis, particularly the glans penis. When the pudic nerve is sectioned, stimulation of the glans no longer results in erection and ejaculation. The act of ejaculation probably starts in the vasa efferentia and epididymis and travels along the ducts deferens. At the same time the muscular walls of the accessory sexual glands are contracting, forcing the accessory fluids into the pelvic urethra. The urethra is emptied through rhythmic contraction of the urethral, ischiocavernosus, and bulbocavernosus muscles.

The Semen. The amount of semen ejaculated at one time varies greatly with the species and also with the individual. The amount increases after a period of sexual rest. It is much reduced in animals in continuous service. The number of spermatozoa suspended in the liquid portion of the semen also varies greatly. Lewis found that the density of sperm suspension and also the amount of semen decreased following daily services in the stallion but increased again a few days after the animal was taken out of service. In one stallion given one service per day for nine days, the amount of semen decreased from 65 cc. on the first service to 5 cc. on the ninth. After several days of sexual rest, 60 cc. of semen were again collected from the stallion. The number of spermatozoa also gradually decreased from 131,750 to 5,840 per cu. mm. of semen from the first to the last service. In another stallion the spermatozoa decreased from 232,500 to 43,000 per cu. mm. after service once daily for eleven days. The spermatozoa showed a much shorter life span following continuous service. Polowzow reports that immature sperms appear in the semen of stallions in daily use, but normal sperms after a rest period of 48 hours. Lewis records the number of spermatozoa in the semen of the boar as varying from 365,000 to 600,000 per cu. mm. The amount of semen ejaculated by the dog may vary from 0.5 cc. to 30 cc. or more, depending upon the size and condition of the dog. In the ram the amount is usually small, 0.5 cc. to 5 cc. The stallion may ejaculate 100 cc. or even 300 cc. following periods of sexual rest. The boar may produce as much as 350 cc. of semen, while the bull usually produces 5 cc. or more.

The number of spermatozoa in a normal ejaculation is about 4,000,000,000, but considerable variation from this round figure may be expected. The number does not differ greatly from species to species; almost all of the differences in the amount of semen is due to the bulk of secretion from the accessory glands. A good specimen of semen contains very few dead sperms when it is examined under the microscope just after collection, and the activity should be intense. Examination should be done at a temperature of 30 degrees C. or a little higher, and if the specimen is diluted this should be done with isotonic saline solution. The condition of the spermatozoa is best judged by the examination of stained specimens. A bead of protoplasm on the tail-piece denotes immaturity. Sterility, whether complete or partial, is correlated to a high degree with the shape of the sperm heads. Over 20 per cent of abnormal sperms is strongly presumptive of sterility. The most dangerous forms are those with narrow or pear-shaped heads. Coiled tails are also frequently met with in samples of poor semen.

The physical nature of semen differs greatly in different animals depending on the size and degree of activity of the accessory glands. It is, as a rule, a rather thick, whitish or yellowish-white, opaque fluid tending to liquefy after standing. The odor is characteristic, but varies greatly with the species. The reaction is alkaline. In those animals in which an analysis of the semen has been made, the amount of water varies from 97.5 per cent in the dog to 90.3 per cent in man. The ash varies from 0.6 to 0.9 per cent; organic matter, 1.2 to 8.7 per cent; and lipoids, 0.18 to 0.2 per cent. Protein varies from 1.25 to 2.85 per cent and consists of albumins, globulins, nucleoproteins, mucin, and albumoses. The ash contains large amounts of calcium and phosphoric acid. The organic matter in the semen, exclusive of the cellular elements, which consist of spermatozoa and a few lymphocytes, contains both amorphous and crystalline substances. The amorphous substances are largely albuminous granules, fat globules, and lipoids. If fresh semen is spread upon a glass slide and allowed to stand, characteristic crystals of spermine phosphate appear. Prostatic secretion is very rich in spermine phosphate, and the prostate is thought to be the source of its secretion in semen. The fact that it has not been found in the semen of the bull adds to this belief, as the prostate is very rudimentary in this animal. Spermine is an organic ammonium base and is not essential to fertilization. It is not confined to the gonads, as it has been found in many other organs of the body. Its function, if any, is unknown.

The head of the spermatozoon is a nucleus and, like all cell nuclei, is made up principally of nucleoprotein. The nucleic acid component seems to be constant and is the same as that found in other cells, but the protein component varies with the species. The chemistry of spermatozoa has been studied more carefully in fishes than in other animals because of the ease with which spermatozoa may be obtained in quantity. In the spermatozoa of many fishes protamines are the most important protein constituents; the exact nature of the protamine varies in the different species. Protamines are strong bases and yield but few amino acids when broken down. In some species of fishes more complex proteins, histones, containing a larger number of amino acids, are found in the spermatozoa.

Coition. The act of coition or coitus is of very short duration in the bull and ram, consuming but a few seconds of time. It is somewhat longer in the stallion and jack. It usually consumes several minutes in the boar. In the dog it consumes 15 to 30 minutes. The bulbus glandis of the dog is very slow in erection. It becomes very large and dilates the posterior portion of the vagina, which is correspondingly large to receive it. At the same time the sphincter of the vagina contracts and the male is unable to withdraw the penis in the erect state.

Insemination. In the ram and the goat the processus urethrae is believed by many to be for the purpose of placing the semen in the cervical canal. Its removal diminishes, but does not altogether destroy, the fertility of the male. In the stallion the free portion of the erect penis is nearly twice as long as the normal vagina of the mare. Thus the vagina is stretched, the large corona glandis is placed against the external os, and ejaculation may take place directly into the cervical canal. Much of the semen, probably most of it, drops back into the vagina and is expelled through the vulva. The penis of the bull is also much longer than the vagina of the cow. The cervix is sufficiently relaxed to allow the glans penis, driven with such force as it is in the bull, to enter the os. Mucus and semen are commonly discharged from the vulva in the cow in copious quantities following service. The penis of the bull very commonly lacerates the wall of the vagina during service. This is particularly true with mature males. Small quantities of blood may be seen exuding from the injured surface and should not be mistaken for postestrous bleeding, in which instance the blood is from the uterus and not the vagina. In the dog ejaculation is thought to take place after the bulbus glandis has become enlarged and the organ cannot be withdrawn from the female passage. However, dogs have been known to inseminate females successfully in cases where the penis was withdrawn before enlargement of the bulbus glandis took place. The small twisted extremity of the penis of the boar probably readily enters the cervical canal of the sow during coition. Some semen may enter the body of the uterus in Equidae at the time of service, but in other species, with the possible exception of sows, semen is deposited either in the posterior part of the cervical canal or in the anterior part of the vagina around the external os. Practically all the semen is found in the anterior part of the vagina immediately following service. It must be pointed out, however, that our knowledge of the internal relations of the organs during coitus is mainly conjectural.

There is little doubt that successful coitus is accomplished only when semen is placed directly in the os or else directly upon the external os. Artificial insemination has never been sufficiently successful to be considered practical when the semen is placed in the vagina. It must be introduced into the os or into the body of the uterus itself. The vaginal secretions are somewhat toxic to spermatozoa. Spermatozoa from bulls of known fertility have been found to survive, that is, show activity, in normal vaginal secretions for only ¾ to 1½ hours. Human spermatozoa live only about one hour in the vagina.

Passage of Sperm Through the Female Tract. It has just been noted that the sperm has little chance to survive if it does not gain ready access to the uterus. Lewis records one case in which live spermatozoa were found in the lower third of the oviduct of a sow 7½ hours after breeding and another case in which they were present throughout the uterus but not in the oviduct 4 hours after breeding. Hartman and Ball bred rats, destroyed the female immediately after breeding, and clamped off the uterus. By this experiment they determined that spermatozoa may reach the uterine tube in the female in less than one minute following service. It is not probable that spermatozoa can traverse the long uterus of the sow (about 4 feet) in 4 hours by their own movement, nor that they can do so in the rat in one minute. The uterus of the female is highly congested and edematous during heat, and the cavity contains a small amount of fluid. Muscular activity is at its height also at this time (see previous chapter). Direct injection of semen into the uterus, together with muscular action by this organ and by the oviducts, probably gives considerable help to the spermatozoa during their passage up the female tract. In most species fertilization of the egg takes place in the ampulla or in the upper third of the oviduct.

Longevity of Germ Cells. By destroying sows at varying periods after they had been bred and examining the genital tract for spermatozoa, Lewis found sperms to be abundant in the uterus shortly after breeding, but they tended rapidly to disappear, so that the day following only a few cells could be found. At first a large precentage of the cells showed activity. This, however, was very rapidly lost. As a rule, all cells were dead, that is, inactive, after 20 hours, although he records one case where cells were found alive 41½ hours after breeding. Lewis determined that the sow ovulates toward the end of the heat period. He succeeded in breeding sows while out of heat. By doing this he hoped to prove whether or not the sperm could live long in the female tract under natural conditions. Sows were bred at all times between the heat periods. In no case did a sperm cell survive until the following heat period and fertilize the eggs of that period. Lewis concluded that the sperm cells could not survive more than a few hours (possibly not over 24, as a rule) in the genital tract of the sow, and that they tended rapidly to disappear, but he did not determine by what means they were destroyed. Aitken bred a mare on the first day of heat to a stallion that had not seen service over twice a month. The mare was not bred again. She ovulated on the sixth day of heat and conceived; thus the sperms must have lived five days, but this is probably not the rule. Conditions in this experiment were ideal, as the stallion was not overworked.

Hammond and Asdell found that the sperm may remain alive in the epididymis of a rabbit and be capable of fertilizing the egg for a period of 38 days. The upper portion of the epididymis was tied off to avoid new introduction of sperms from the testicle. On the other hand, they found that the sperm lived only 30 hours in the female tract in a functional condition, that is, capable of fertilizing the ovum. Spermatozoa have been recorded as showing activity in the female organs of the dog and rabbit for one week after coitus, but this does not indicate that they were capable of fertilizing the egg.

Experiments carried out to date would indicate that the spermatozoon in domestic mammals retains its fertility but one or two days in the female genital tract under ordinary conditions.

It is reported that two or more days are required after mating before fertile eggs are laid by the chicken, and that the eggs may be fertile for 15 days after the last mating; but to insure high fertility hens must be mated every other day.

With reference to the longevity of the egg in mammals, Hartman (1924) has well stated the prevailing opinion among embryologists: "The egg cannot wait long for the spermatozoa—these must be on hand when ovulation takes place. It seems probable that hours, not days, measure the delay that results in sterile coitus." Lewis bred sows out of heat and determined that only two out of seven conceived when bred the day following heat. None conceived out of 24 bred at later dates. Since the sow ovulates in late estrus, this would indicate that the extreme life of the egg is not over 24 hours. Hammond and Marshall have found that the rabbit's egg is capable of being fertilized only for 2 to 4 hours after it has been shed. Circumstantial evidence makes us believe that this period is not far from the truth in all domestic animals. But Evans and Cole have produced evidence to show that the ovum of the dog may be fertilized for at least 4 days after it has been shed. It must be remembered, however, that the dog, and also the fox, are quite exceptional in that the egg is not mature at the time it is shed.

ARTIFICIAL INSEMINATION

Artificial insemination is a specialized technic which has been much developed during the past few years. Several methods have been tried for the collection of the semen. The first of these, an old method, is to collect the semen in a sponge placed in the vagina before service. This, and any other method of collection from the unprotected vagina, has the disadvantage that the semen is mixed with copious vaginal secretions which reduce the life of the sperms. Bacterial contamination is also present. In the sponge method it is most difficult to recover the sperms without damaging their tails. The newer methods in use are designed to collect specimens without these disadvantages. One such method is to use the sperm collector, a rubber sleeve kept in position by an inflated ring, with an outer protection to cover the anus and escutcheon. The usual method employs the artificial vagina, a water-jacketed rubber sleeve which is placed on the erect penis as the male mounts the female. Ejaculation takes place into this apparatus held below or to one side of the female and the penis does not enter the vagina. Other methods use a dummy animal with an artificial vagina which is served as though the dummy were a female. There is some evidence that, unless allowed frequent normal copulations, the bull repeatedly subjected to these technics loses interest and becomes spoiled for reproductive purposes. Electrical stimulation of the lumbar region of the spinal cord of the male has also been employed to promote ejaculation. Semen may be collected from the rooster by massaging the ejaculatory ducts through the abdomen.

When a good sample of semen has been obtained, it may be preserved by covering the specimen with a layer of mineral oil. This imprisons the CO_2 produced by metabolic activity and thus immobilizes the sperms. The optimum temperature for storage is about 8 degrees C. Before use the semen should gradually be brought to body temperature. At higher temperatures the movement of the sperms is so rapid that they soon use up their small store of energy and die. At lower temperatures some unknown factor impairs their survival. According to Walton, at least a million spermatozoa must be used in one artificial insemination to give a chance of fertilization. He has kept semen for a week before its fertilizing power was entirely lost.

The keeping qualities of semen are inversely proportional to the amount of the secretions from the accessory glands. Hence stallion's semen and boar's semen do not retain their fertility for more than a few hours. Concentration of the spermatozoa may be made by collecting only the richest fractions of the ejaculate or by careful centrifuging.

The ejaculate may be diluted before preservation or before use so that it can be divided to inseminate a larger number of females. The most satisfactory diluter for general use is the following, which has been developed by Lardy and Phillips:

100 cc. boiling distilled water
0.2 gm. KH_2PO_4
2.0 gm. $Na_2HPO_4 \cdot 12H_2O$

After the solution has cooled, an equal volume of fresh hen's egg yolk is added. Detailed information on the methods used in artificial insemination have been given by Perry. Critical methods have been evolved for the determination of the keeping qualities and potential fertility of the semen from bulls (Willett and Salisbury).

The semen, diluted or undiluted, should not be placed in the vagina but within the lips of the os uteri, otherwise the insemination usually fails. In the mare the sample may be injected some distance, and in the cow a careful operator may work the insemination tube past the complicated series of folds in the cervix. Sterile precautions should be observed in all artificial insemination work. In species whose ovulation time lies within the heat period it is useless to inseminate after heat has passed, but the cow, with ovulation averaging about thirteen hours after the end of heat, may be inseminated with a reasonable degree of success during the first eight hours after heat is past. (See Fig. 179, p. 763.)

A number of control measures have been devised for use in artificial insemination practice. It is important to know the number of active spermatozoa in an ejaculate so that the proper degree of dilution is not exceeded. The time-consuming method of direct counts has been superseded by turbidity tests in which the reduction of the amount of light that will pass through the semen is used as an index of the number of spermatozoa. Activity is measured by oxygen consumption—the time taken to decolorize a given amount of methylene blue. Periodic examination must be made of samples to insure that sufficient activity exists and that the count of abnormal spermatozoa does not rise too high.

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Chapter XLI

GROWTH

PROBLEMS relating to growth have attracted much attention during the past few years, and, in view of the economic importance of this branch of physiology, a short summary of the more striking results obtained are given.

The fertilized ovum is about the same size in all mammals. In the dog it is about 0.1 mm. in diameter, in the pig 0.11 mm., in the cow 0.12 mm., in the mare 0.13 mm., and in the ewe 0.14 mm. As the egg travels through the oviduct it divides but does not increase in size, so that the individual cells are smaller than the original egg. In the uterus nutritive substances are absorbed from the uterine milk secreted by the glands of the endometrium, and growth in size begins. Each cell division, that is, from the single cell to the two-cell stage, to the four-cell stage, etc., takes about a day in the early stages. By the fourth division, species differences begin to show (Fig. 182). The pig, which is characterized by rapid growth, continues at a greater rate than the bovine and sheep. Subsequent growth continues to be rapid in the pig, is slower in the bovine, and is very slow in the horse and sheep.

The ovum has developed all the systems, vascular, muscular, etc., during the first few weeks of pregnancy (within the first two months in the bovine), and, after this, growth consists largely of increases in length and weight; differentiation has been completed. Birth causes a temporary check, soon recovered from, and growth in weight then proceeds in an orderly way. At first the absolute increase in weight is small, but each increase provides more cells which can divide so that the growth curve becomes steeper. The percentage increase is fairly constant and is characteristic of the species. It remains so until about two-thirds of the mature weight is reached. Then the amount of weight gained in unit time decreases rapidly, but, again, the percentage rate of decrease is fairly constant, and is characteristic for the species. The consequence of the action of the two factors—constant percentage increase in weight and constant percentage decrease in weight gained in unit time—is that the growth curve is somewhat S-shaped. If, instead of plotting weight against time, the logarithm of weight is plotted against time, the period of growth-rate increase is shown as a straight line subtending a large angle to the base line and the period of decrease as a straight line subtending a smaller angle. The point of inflection of the two lines gives a point of change. This point is roughly the time at which puberty occurs. The two methods of plotting growth data are illustrated by the example for the cow in Figs. 183 and 184.

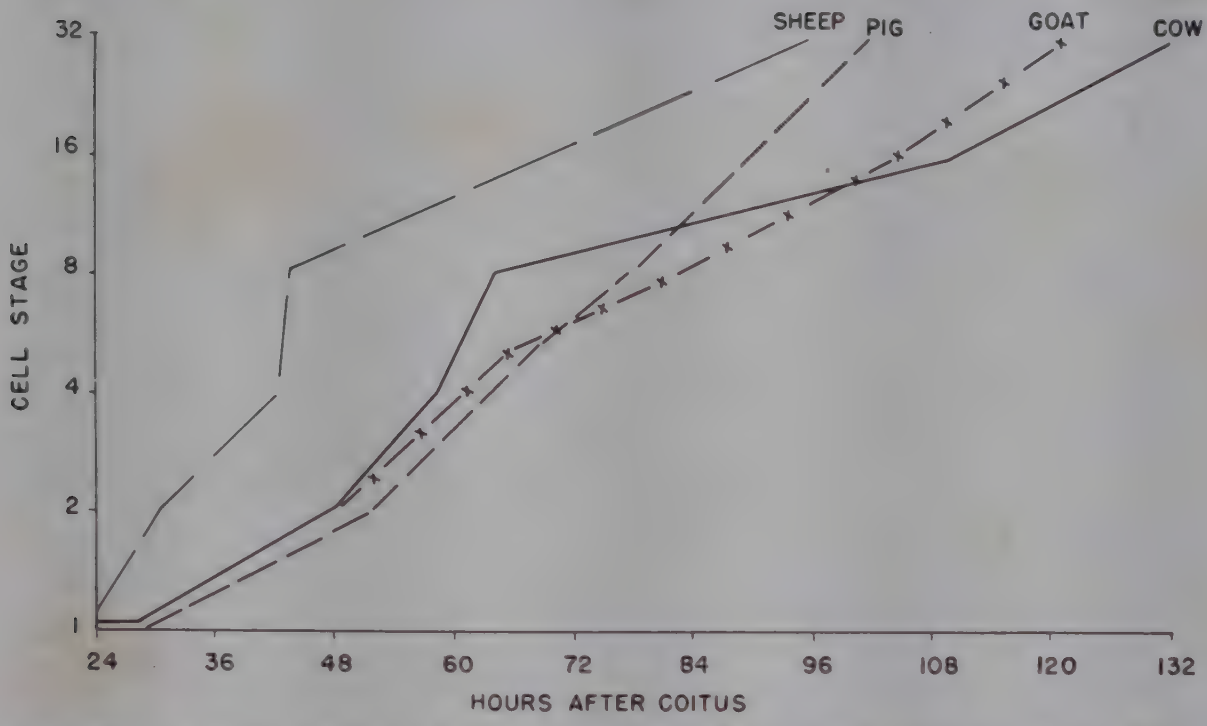

FIG. 182.—Relative growth of early embryos of domestic animals. (Data from Asdell, *Journal of Gerontology*, 1946, **1**, 224, and Amoroso, Griffiths, and Hamilton, *Journal of Anatomy*, 1942, **76**, 377.)

The shape of growth curves is such that by adjusting the weight and time scales in graphs the curves may be made to fit one another with a considerable degree of accuracy. Man is the only known exception. When other species are growing rapidly he grows relatively slowly, and when they slow down he begins to grow more rapidly and delays his final slowing. This produces a long adolescent period, and it accounts, in some measure, for the greater response of man to education.

Growth is, to a large extent, under the control of the endocrine glands. Thyroxine is necessary that it may occur at all, and the growth hormone of the anterior pituitary determines its extent, but it can only occur while the epiphyses of the bones are still open. As different parts of the skeleton vary in their ability to respond to growth hormones at any given time, gradients are set up which cause the body proportions to vary with age. One gradient affects the axial skeleton and its degree of action is most intense at first in the region of the head, but as the age increases the degree of intensity proceeds toward the tail. Thus, in early embryonic life the head is enormous compared with the rest of the body, and it is still relatively large at birth. Another gradient affects the appendicular skeleton, and the impulse proceeds from the extremities toward the body. For this reason young animals are relatively long-legged and short-bodied. The bones of the trunk are the last to receive the accelerations, so that their rapid development is reached late in the growth period. In this manner the length and solidity of the adult are produced.

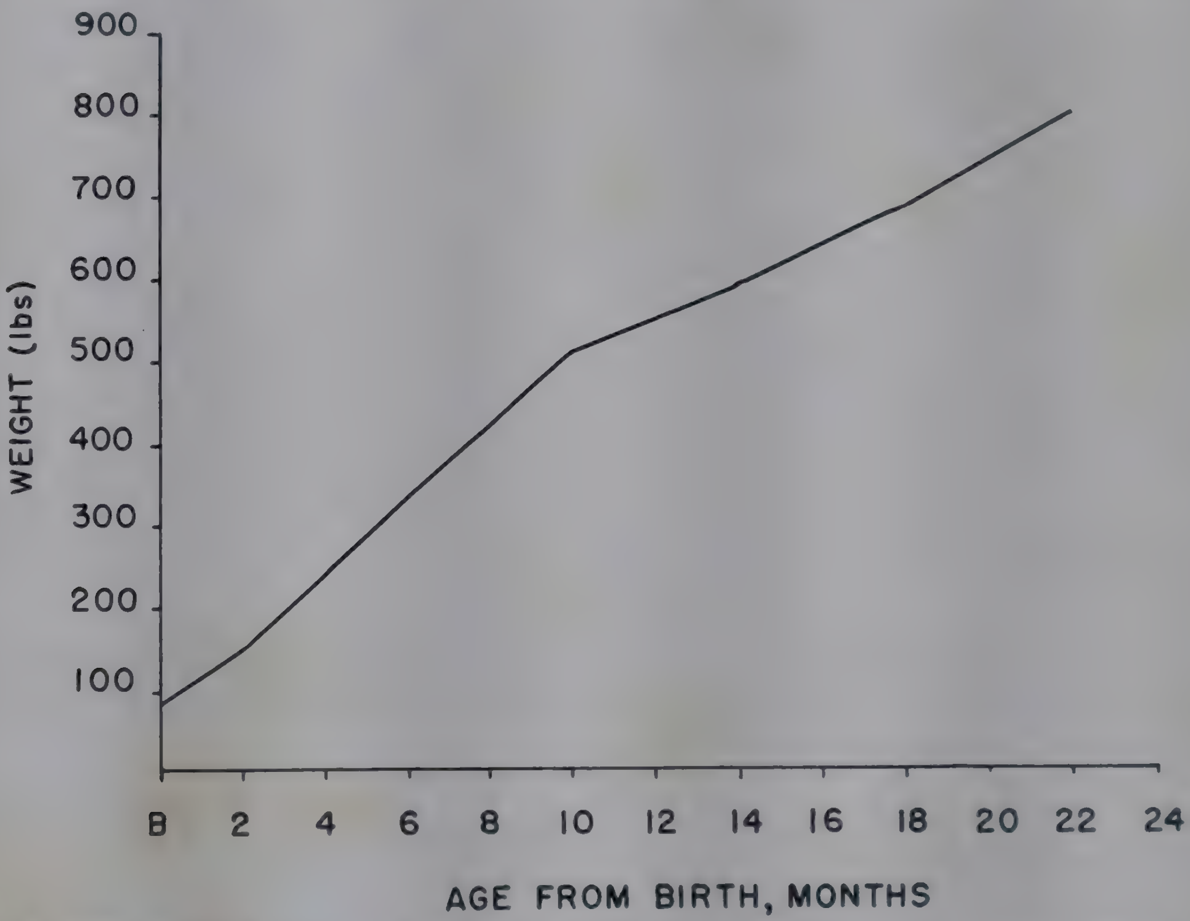

FIG. 183.—Growth curve of Holstein heifers from birth to 24 months. The S shape would be more evident if the data began at conception. Plotted on arithmetic scale. (Data from Brody, *Missouri Agricultural Experiment Station Research Bull.* 96, 1926.)

Estrogens, produced by the ovary after puberty has been reached, cause rapid closing of the epiphyses. Thus growth tends to cease earlier in the female than in the male. The result is that the female is, on the average, a little smaller than the male in any species. If the secretion of estrogens is prevented by ovariectomy, the female grows more rapidly and reaches a greater size than she would do otherwise. Pregnancy, by the action of progesterone in inhibiting estrogens, causes a resumption of growth so that an animal which has been pregnant usually reaches a greater size than one which has not been bred.

Besides the skeletal-growth gradients there are others which are important. Bone growth is, in general, more intense in early life; then muscular development takes priority. Later the deposition of fat is the main type of growth. It is not easy to fatten an animal while bone or muscular growth has priority. In view of this, Hammond has suggested that it should be possible to vary the proportion of bone, muscle, and fat in the carcass by feeding lightly or heavily at the appropriate time, and his experiments have borne this out. Light feeding in the period just before and after weaning has produced pigs with light bone. By increasing the feed before the usual time for fattening, the proportion of muscle has been increased and heavier cuts have been obtained as a consequence. These methods of modifying the carcass have been successful when the pigs were individually fed, but in mass feeding it would be difficult to insure that each animal eats its proper ration.

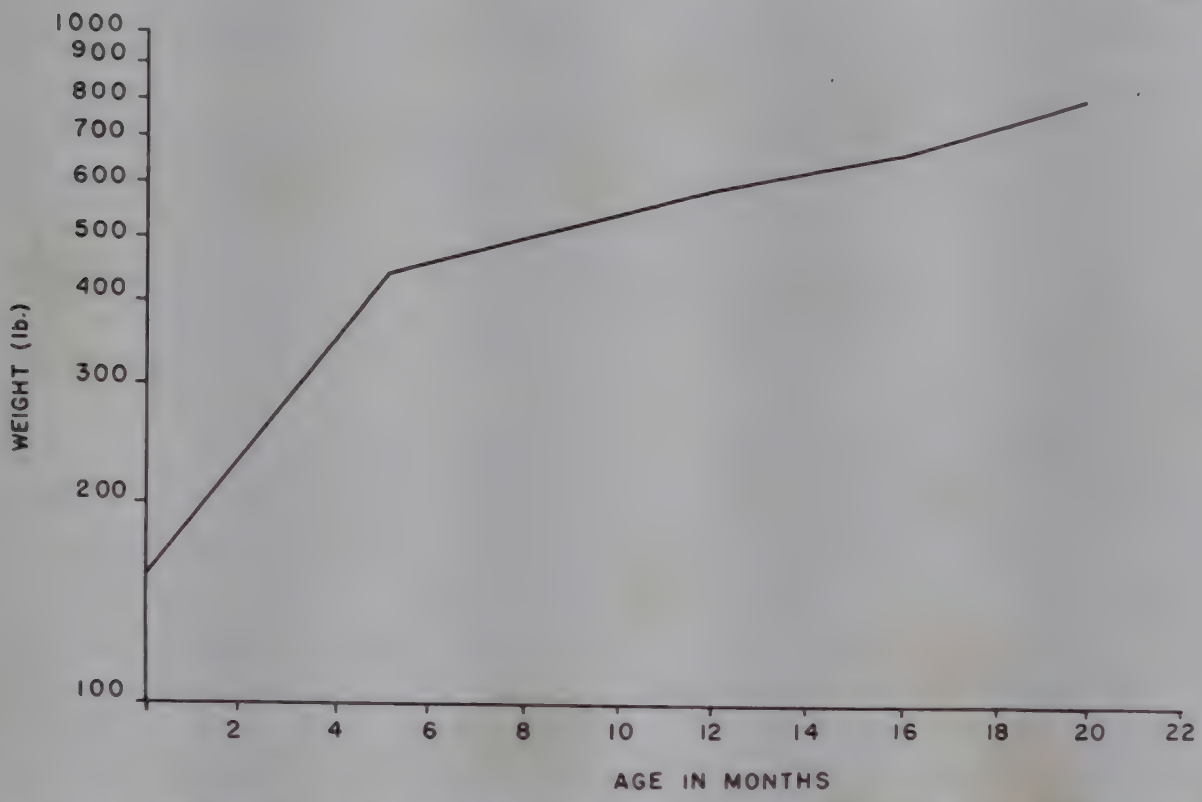

FIG. 184.—The data of Fig. 183 plotted with weight on a logarithmic scale. The slope of the line indicates the intensity of the growth stimulus. The inflection occurs near the age of puberty.

Quality in meat is a somewhat indefinite factor to evaluate. The size of individual muscle fibers affects quality to some extent. In general, the larger the fibers, the coarser the meat. The proportion of muscle cells to tendinous attachments is another factor, and the amount of fat is a third, perhaps the most important of all. Fat is deposited between the muscle fasciae, and it accumulates in greatest amount along the courses of the larger blood vessels. It is also deposited between the muscle cells, producing the desirable factor known as marbling, and also within the cells. In general, quality increases until there is about 40 per cent of fat in the boneless cut. After this amount has been reached, an addition of one or two per cent causes a rapid deterioration. The improvement of quality with fattening is easily upset if the animal becomes too fat.

The order of deposition of fat follows a definite pattern. Marbling appears earliest in the rib and loin cuts, latest in the leg and shoulder cuts. The quality of the fat deposited varies with the feed. If the fat in the feed has a low melting point, the body and muscular fat may be unpleasantly fluid. Fat made in the body by feeding carbohydrate tends to be harder and to be more nearly the type most suitable in the finished carcass (Chapter XXV).

Efficiency of Production. The efficiency of production is an important factor in determining the type of animal husbandry which should be followed, particularly in times of feed shortages, such as those which were encountered in World War II. Pigs and poultry were largely eliminated in some countries, since they depend in no small measure upon foods which can be consumed by man. Sheep were retained in spite of their low efficiency because they do not compete with man, but, instead, convert low-quality roughages which man cannot consume, into muscle and fat which are valuable to him. Cattle use higher-quality feeds, but because of the greater efficiency of the dairy cow and the great value of milk for feeding infants and children, the dairy cow was favored above the beef animal. The following table is an indication of the relative efficiency of livestock as converters of food.

EFFICIENCY OF LIVESTOCK AS CONVERTERS OF FOOD

Type of Stock	Percentage of Feed Made Available for Human Consumption	
	Energy	Protein
	per cent	*per cent*
Dairy cattle	17.5	30
Beef steers	4–14	3–13
Hogs	25	12
Sheep	10	5

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